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FORM PTO-1390 (REV 11-98)

U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U S APPLICATION NO (If known see 37 CFR 1 5)
11034US02 / 100-248.P1	09/446415

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US98/13007	22 June 1998	20 June 1997

TITLE OF INVENTION Bactericidal/Permeability-Increasing Protein: Crystallization, X-Ray Diffraction, Three-Dimensional Structure Determination, Rational Drug Design & Molecular Modeling of Related Proteins

APPLICANT(S) FOR DO/EO/US
Lesa J. Beamer, Stephen F. Carroll and David Eisenberg

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND or SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c [X] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [ ] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information:
    Computer readable copy of sequence listing containing nucleotide and/or amino acid sequence and Statement Under 37 C.F.R. 1.821; Verified Statement Claiming Small Entity Status; Filing fee ($945.00); Return postcard

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U.S. APPLICATION NO (if known see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/446415		

17. [X] The following fees are submitted:	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5))		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$970.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$840.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$760.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(l)-(4) **$670.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$96.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 970.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(c)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	25 -20 =	5	X $18.00	$ 90.00	
Independent claims	13 -3 =	10	X $78.00	$ 780.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+$260.00	$ 260.00	
TOTAL OF ABOVE CALCULATIONS =				$ 1,050.00	
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28).				$ 1,050.00	
SUBTOTAL =				$ 1,050.00	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$ 1,050.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$ 945.00	
				Amount to be: refunded	$
				charged	$ 105.00

a. [X] A check in the amount of $ 945.00 to cover the above fees is enclosed.

b. [X] Please charge my Deposit Account No. 13-0017 m the amount of $ 105.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-0017 A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

Janet M. McNicholas
SIGNATURE

Janet M. McNicholas
NAME

32,918
REGISTRATION NUMBER

PATENT

Attorney's Docket No: 11034US02 / 100-248.P1

Applicant or Patentee: Beamer, et al.

Serial or Patent No:

Filed or Issued:

For: BACTERICIDAL/PERMEABILITY-INCREASINGPROTEIN: CRYSTALLIZATION, X-RAY DIFFRACTION, THREE-DIMENSIONAL STRUCTURE DETERMINATION, RATIONAL DRUG DESIGN AND MOLECULAR MODELING OF RELATED PROTEINS

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) and 1.27(c)) -- SMALL BUSINESS CONCERN

I hereby declare that I am

☐ The owner of the small business concern identified below:

☒ An official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN XOMA Technology Ltd.

ADDRESS OF BUSINESS 2910 Seventh Street
Berkeley, CA 94710

I hereby declare that the above-identified small business concern qualifies as a small business concern as defined in 13 CFR 121.12, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third-party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to, and remain with, the small business concern identified above with regard to the invention, entitled BACTERICIDAL/PERMEABILITY-INCREASINGPROTEIN: CRYSTALLIZATION, X-RAY DIFFRACTION, THREE-DIMENSIONAL STRUCTURE DETERMINATION, RATIONAL DRUG DESIGN AND MOLECULAR MODELING OF RELATED PROTEINS by inventor(s) Beamer, Carroll and Eisenberg described in

☒ The specification filed herewith.

☐ Application Serial No. _____, filed _____.

☐ Patent No. _____ , issued _____.

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If the rights held by the above-identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9(d) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

*NOTE: *Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27).*

NAME: _____

ADDRESS: _____

☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

NAME: _____

ADDRESS: _____

☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b)).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING: Janet M. McNicholas

TITLE OF PERSON OTHER THAN OWNER: Assistant Secretary

ADDRESS OF PERSON SIGNING: XOMA Technology Ltd.
2910 Seventh Street
Berkeley, CA 94710

SIGNATURE Janet M. McNicholas Date: December 20, 1999

BACTERICIDAL/PERMEABILITY-INCREASING PROTEIN: CRYSTALLIZATION, X-RAY DIFFRACTION, THREE-DIMENSIONAL STRUCTURE DETERMINATION, RATIONAL DRUG DESIGN AND MOLECULAR MODELING OF RELATED PROTEINS

This is a continuation-in-part application of U.S. Application Serial No. 08/879,565, filed June 20, 1997, which is hereby incorporated by reference in its entirety.

The present invention generally pertains to the fields of protein crystallization, x-ray diffraction analysis, three-dimensional structural determination, rational drug design and molecular modeling of related proteins. The present invention solves the three-dimensional structure of bactericidal/permeability-increasing protein (BPI) and provides crystallization methods for BPI protein products. A crystallized BPI protein product was physically analyzed by x-ray diffraction techniques. The resulting x-ray diffraction patterns were of sufficiently high resolution to be useful for determining the three-dimensional structure of BPI and have yielded atomic coordinates for BPI. The present invention relates to uses of BPI coordinates for molecular modeling of related proteins and rational drug design (RDD) of mimetics and ligands for BPI and for related proteins. The present invention also relates to atomic coordinates of BPI, or portions thereof, to solve crystal forms of BPI proteins or their fragments, analogs, and variants thereof, or of related proteins, including lipid transfer proteins, or their fragments, analogs and variants.

Part of the work performed during development of this invention utilized U.S. Government funds. The U.S. Government has certain rights in this invention.

Background of the Invention

Bactericidal/permeability-increasing protein (BPI) is a protein isolated from the granules of mammalian polymorphonuclear leukocytes (PMNs or neutrophils), which are blood cells essential in the defense against invading microorganisms. BPI is known to bind the lipopolysaccharide (LPS), a major component of the outer membrane of gram-negative bacteria that stimulates a potent inflammatory response. Human BPI protein has been isolated from PMNs by acid extraction combined with either ion exchange chromatography [Elsbach, *J. Biol. Chem.*, *254*:11000 (1979)] or *E. coli* affinity chromatography [Weiss, et al., *Blood*, *69*:652 (1987)]. BPI obtained

in such a manner is referred to herein as natural BPI and has been shown to have potent bactericidal activity against a broad spectrum of gram-negative bacteria. The molecular weight of human BPI is approximately 55,000 daltons (55 kD). The amino acid sequence of the entire human BPI protein and the nucleic acid sequence of DNA encoding the protein have been reported in Figure 1 of Gray et al., *J. Biol. Chem.*, *264*:9505 (1989), incorporated herein by reference. The Gray et al. amino acid sequence is set out in SEQ ID NO: 1 hereto. U.S. Patent No. 5,198,541, EP0375724 and WO89/10486 (PCT/US88/02700) disclose recombinant genes encoding and methods for expression of BPI proteins, including BPI holoprotein and fragments of BPI.

A proteolytic N-terminal fragment of BPI having a molecular weight of about 25 kD possesses essentially all the anti-bacterial efficacy of the naturally-derived 55 kD human BPI holoprotein. [Ooi et al., *J. Bio. Chem.*, *262*: 14891-14894 (1987)]. In contrast to the N-terminal portion, the C-terminal region of the isolated human BPI protein displays only slightly detectable anti-bacterial activity against gram-negative organisms. [Ooi et al., *J. Exp. Med.*, *174*:649 (1991).] An N-terminal BPI fragment of approximately 23 kD, referred to as "$rBPI_{23}$," has been produced by recombinant means and also retains anti-bacterial activity against gram-negative organisms. [Gazzano-Santoro et al., *Infect. Immun. 60*:4754-4761 (1992).] An N-terminal analog of BPI, $rBPI_{21}$, has been produced as described in Horwitz et al., *Protein Expression Purification, 8*:28-40 (1996).

The bactericidal effect of BPI has been reported to be highly specific to gram-negative species, e.g., in Elsbach and Weiss, *Inflammation: Basic Principles and Clinical Correlates*, eds. Gallin et al., Chapter 30, Raven Press, Ltd. (1992). This reported target cell specificity was believed to be the result of the strong attraction of BPI for LPS on the outer membrane (or envelope) of gram-negative organisms. Although BPI was commonly thought to be non-toxic for other microorganisms, including yeast and for higher eukaryotic cells, it has recently been discovered that BPI protein products exhibit activity against gram-positive bacteria, mycoplasma, mycobacteria, fungi, protozoa and chlamydia.

The precise mechanism by which BPI kills gram-negative bacteria is not yet completely elucidated, but it is believed that BPI must first bind to the surface of the

bacteria through electrostatic and hydrophobic interactions between the cationic BPI protein and negatively charged sites on lipopolysaccharide. Bacterial LPS has been referred to as "endotoxin" because of the potent inflammatory response that it stimulates, i.e., the release of mediators by host inflammatory cells which may ultimately result in irreversible endotoxic shock. BPI binds to lipid A, reported to be the most toxic and most biologically active component of LPS.

In susceptible gram-negative bacteria, BPI binding is thought to disrupt LPS structure, leading to activation of bacterial enzymes that degrade phospholipids and peptidoglycans, altering the permeability of the cell's outer membrane, and initiating events that ultimately lead to cell death. [Elsbach and Weiss (1992), *supra*]. BPI has been proposed to act in two stages. The first stage proposed is a sublethal one that is characterized by immediate growth arrest, permeabilization of the outer membrane and selective activation of bacterial enzymes that hydrolyze phospholipids and peptidoglycans. Bacteria at this stage could be rescued by growth in serum albumin supplemented media [Mannion et al., *J. Clin. Invest.*, *85*:853-860 (1990)]. The second stage, defined by growth inhibition that cannot be reversed by serum albumin, is proposed to occur after prolonged exposure of the bacteria to BPI and characterized by extensive physiologic and structural changes, including apparent damage to the inner cytoplasmic membrane.

Initial binding of BPI to LPS leads to organizational changes that probably result from binding to the anionic groups of LPS, which normally stabilize the outer membrane through binding of Mg^{++} and Ca^{++}. Attachment of BPI to the outer membrane of gram-negative bacteria produces rapid permeabilization of the outer membrane to hydrophobic agents such as actinomycin D. Binding of BPI and subsequent gram-negative bacterial killing depends, at least in part, upon the LPS polysaccharide chain length, with long O-chain bearing, "smooth" organisms being more resistant to BPI bactericidal effects than short O-chain bearing, "rough" organisms [Weiss et al., *J. Clin. Invest. 65*: 619-628 (1980)]. This permeabilization of the gram-negative outer envelope is reversible upon dissociation of the BPI, a process requiring high concentrations of divalent cations and synthesis of new LPS [Weiss et al., *J. Immunol. 132*: 3109-3115 (1984)]. Loss of gram-negative bacterial viability, however, is not reversed by processes which restore the envelope integrity,

suggesting that the bactericidal action is mediated by additional lesions induced in the target organism and which may be situated at the cytoplasmic membrane (Mannion et al., *J. Clin. Invest. 86*: 631-641 (1990)). Specific investigation of this possibility has shown that on a molar basis BPI is at least as inhibitory of cytoplasmic membrane vesicle function as polymyxin B but the exact mechanism as well as the relevance of such vesicles to studies of intact organisms was not elucidated (In't Veld, et al., *Infection and Immunity 56*: 1203-1208 (1988)).

BPI is a member of a gene/protein family of lipopolysaccharide binding and lipid transfer proteins whose other currently known members include lipopolysaccharide binding protein (LBP), cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP).

BPI protein products (which include naturally and recombinantly produced BPI protein; natural, synthetic, and recombinant biologically active polypeptide fragments of BPI protein; biologically active polypeptide variants of BPI protein or fragments thereof, including hybrid fusion proteins and dimers; biologically active polypeptide analogs of BPI protein or fragments or variants thereof, including cysteine-substituted analogs; and BPI-derived peptides) have been demonstrated to have a variety of beneficial activities. BPI protein products are known to be bactericidal for gram-negative bacteria, as described in U.S. Patent Nos. 5,198,541 and 5,523,288, both of which are incorporated herein by reference. BPI protein products are also known to enhance the effectiveness of antibiotic therapy in gram-negative bacterial infections, as described in U.S. Patent No. 5,523,288 and corresponding International Publication No. WO 95/08344 (PCT/US94/11225), which are incorporated herein by reference. BPI protein products are also known to be bactericidal for gram-positive bacteria and mycoplasma, and to enhance the effectiveness of antibiotics in gram-positive bacterial infections, as described in U.S. Patent No. 5,578,572 and corresponding International Publication No. WO 95/19180 (PCT/US95/00656), which are incorporated herein by reference. BPI protein products are further known to exhibit anti-fungal activity, and to enhance the activity of other anti-fungal agents, as described in U.S. Patent No. 5,627,153 and corresponding International Publication No. WO 95/19179 (PCT/US95/00498), and further as described for anti-fungal peptides in co-pending U.S. Application Serial No. 08/621,259 filed March 21, 1996,

which is in turn a continuation-in-part of U.S. Application Serial No. 08/504,841 filed July 20, 1994 and corresponding International Publication Nos. WO 96/08509 (PCT/US95/09262) and WO 97/04008 (PCT/US96/03845), all of which are incorporated herein by reference. BPI protein products are further known to exhibit anti-protozoan activity, as described in U.S. Patent No. 5,646,114 and corresponding International Publication No. WO 96/01647 (PCT/US95/08624), all of which are incorporated herein by reference. BPI protein products are known to exhibit anti-chlamydial activity, as described in co-pending U.S. Application Serial No. 08/694,843 filed August 9, 1996 and corresponding International Publication No. WO 98/06415 (PCT/US97/13810), all of which are incorporated herein by reference. Finally, BPI protein products are known to exhibit anti-mycobacterial activity, as described in co-pending U.S. Application Serial No. 08/626,646 filed April 1, 1996, which is in turn a continuation of U.S. Application Serial No. 08/285,803 filed August 14, 1994, which is in turn a continuation-in-part of U.S. Application Serial No. 08/031,145 filed March 12, 1993 and corresponding International Publication No. WO94/20129 (PCT/US94/02463), all of which are incorporated herein by reference.

The effects of BPI protein products in humans with endotoxin in circulation, including effects on TNF, IL-6 and endotoxin are described in U.S. Patent Nos. 5,643,875 and 5,753,620 and corresponding International Publication No. WO 95/19784 (PCT/US95/01151), all of which are incorporated herein by reference.

BPI protein products are also known to be useful for treatment of specific disease conditions, such as meningococcemia in humans (as described in co-pending U.S. Application Serial No. 08/644,287 filed May 10, 1996 and corresponding International Publication No. WO 97/42966 (PCT/US97/08016), which are incorporated herein by reference), hemorrhagic trauma in humans, (as described in co-pending U.S. Application Serial No. 08/862,785, a continuation-in-part of U.S. Serial No. 08/652,292 filed May 23, 1996, now U.S. Patent No. 5,756,464, and corresponding International Publication No. WO 97/44056 (PCT/US97/08941), all of which are incorporated herein by reference), burn injury (as described in U.S. Patent No. 5,494,896 and corresponding International Publication No. WO 96/30037 (PCT/US96/02349), both of which are incorporated herein by reference),

ischemia/reperfusion injury (as described in U.S. Patent No. 5,578,568, incorporated herein by reference), and liver resection (as described in co-pending U.S. Application Serial No. 08/582,230 filed March 16, 1998 which is a continued prosecution application of the same serial no. filed January 3, 1996, which is in turn a continuation of U.S. Application Serial No. 08/318,357 filed October 5, 1994, which is in turn a continuation-in-part of U.S. Application Serial No. 08/132,510 filed October 5, 1993, and corresponding International Publication No. WO 95/10297 (PCT/US94/11404), all of which are incorporated herein by reference).

BPI protein products are also known to neutralize the anti-coagulant activity of exogenous heparin, as described in U.S. Patent No. 5,348,942, incorporated herein by reference, as well as to be useful for treating chronic inflammatory diseases such as rheumatoid and reactive arthritis, as described in U.S. Patent No. 5,639,727, incorporated herein by reference, and for inhibiting angiogenesis and for treating angiogenesis-associated disorders including malignant tumors, ocular retinopathy and endometriosis, as described in co-pending U.S. Application Serial Nos. 08/435,855, 08/466,624 and 08/466,826, and corresponding International Publication No. WO 94/20128 (PCT/US94/02401), all of which are incorporated herein by reference.

BPI protein products are also known for use in antithrombotic methods, as described in U.S. Patent No. 5,741,779 and corresponding International Publication No. WO97/42967 (PCT/US97/08017), which are incorporated herein by reference.

U.S. Patent Nos. 5,420,019 and 5,674,834 and corresponding International Publication No. WO94/18323 (PCT/US94/01235), all of which are incorporated herein by reference, disclose that the replacement of the cysteine residue at amino acid position 132 or 135 with another amino acid renders the resulting BPI polypeptide resistant to dimerization and cysteine adduct formation. It also discloses that terminating the N-terminal BPI fragment at BPI amino acid position 193 resulted in an expression product with reduced carboxy-terminal heterogeneity.

Because of the multiplicity of valuable activities and uses of BPI protein products as exemplified above, a need continues to exist for new products with structures based on or mimicking a BPI protein product and having one or more of the activities and/or uses of BPI protein products, including use as anti-infective products, including antimicrobial agents (*e.g.*, gram-negative bacteria [U.S. Patent

Nos. 5,198,541 and 5,523,288; WO95/08344 (PCT/US94/11225)] and gram-positive bacteria [U.S. Patent No. 5,578,572; WO95/19180 (PCT/US95/00656)], fungi [U.S. Patent No. 5,627,153; WO95/19179 (PCT/US95/00498)], mycobacteria [EP0690721; WO94/20129 (PCT/US94/02463)] and chlamydia [WO96/01647 (PCT/US95/08624)] and endotoxin binding/neutralizing agents [WO95/019784 (PCT/US95/01151)], and as heparin binding/neutralizing products [U.S. Patent Nos. 5,348,942 and 5,639,727; WO94/20128 (PCT/US94/02401)], including for the neutralization of exogenously administered heparin, inhibition of angiogenesis (normal or pathological) for the treatment of chronic inflammatory disease states, and anticoagulant and thrombolytic agents for the treatment of thrombotic disorders [PCT/US97/08017]. All of the above-listed references regarding biological or functional activities of BPI, as well as therapeutic and diagnostic uses of BPI, are hereby incorporated by reference. One avenue of investigation toward solving the problem of new products based on BPI and fulfilling this need is the determination of the crystal structure of a BPI protein product.

Summary of the Invention

The present invention solves the above problem and fulfills the need for designating and making new and useful products based on BPI. It is an object of this invention to solve the three-dimensional structure of BPI and thereby provide the atomic coordinates (i.e., structure coordinates) of BPI from the analysis of x-ray diffraction patterns of sufficiently high resolution to be useful for determining the three-dimensional protein structure.

It is an object of this invention to provide methods of expressing, purifying and crystallizing bactericidal/permeability-increasing protein (BPI) products, and thereby provide crystallized BPI proteins.

It is an object of this invention to provide the use of the structure coordinates of a BPI crystal to allow the design of compounds for mimicking a BPI protein product to reveal the atomic details of ligand binding sites of BPI (*e.g.* lipid-like or heparin-like molecules).

It is an object of this invention to provide use of the structure coordinates of a BPI crystal as described herein to solve the crystal structure of a crystal of a different BPI protein or fragment, analog or variant thereof, or a crystal of a related

protein, including a BPI-related lipid transfer protein or a fragment, analog or variant thereof.

It is an object of this invention to provide mutants of BPI or fragments, analogs, or variants thereof characterized by one or more different properties as compared with wild-type BPI. These properties include altered surface charge, altered lipid binding pockets, altered specificity or higher activity. BPI mutants are useful to identify those amino acids that are most important for the lipid and heparin binding activity and other biological activities of BPI. This information, in turn, allows the design of new structures with one or more different properties based on BPI.

It is an object of this invention to provide the use of the structure coordinates and atomic details of BPI as described herein or its fragments, analogs or variants (including mutants or co-complexes) or of a BPI-related lipid transfer protein or its fragments, analogs or variants (including mutants or co-complexes) to design, evaluate computationally, synthesize and use new structures based on BPI with desirable properties of BPI, such as physical and pharmacological properties.

X-ray diffraction patterns of a related protein can be analyzed directly to provide the three-dimensional structure (if of sufficiently high resolution), however, the atomic coordinates for the crystallized BPI, as provided herein, can be used for structure determination. The x-ray diffraction patterns obtained by methods of the present invention, and provided on computer readable media, are used to provide electron density maps. The amino acid sequence is also useful for three-dimensional structure determination. The data is then used in combination with phase determination (*e.g.* using multiple isomorphous replacement (MIR) molecular replacement techniques) to generate electron density maps of BPI, using a suitable computer system. The electron density maps, provided by analysis of either the x-ray diffraction patterns or working backwards from the atomic coordinates, provided herein, are then fitted using suitable computer algorithms to generate secondary, tertiary and/or quaternary structures and/or domains of BPI, which structures and/or domains are then used to provide an overall three-dimensional structure, as well as binding and/or active sites of BPI.

It is also an object of this invention to specifically provide for the use of three-dimensional modeling of BPI and other members of the BPI protein family using the coordinates from the x-ray diffraction patterns. The coordinates and amino acid sequences are entered into one or more computer programs for molecular modeling. Such molecular modeling programs generate atomic coordinates that reflect the secondary, tertiary and/or quaternary structures of the protein which contribute to its overall three-dimensional structure and provide information related to binding and/or active sites of the protein.

It is a further object of this invention to specifically provide for the use of similar molecular modeling for rational drug design (RDD) of mimetics and ligands of BPI and other members of the BPI protein family. The drug design paradigm uses computer modeling programs to determine potential mimetics and ligands which are expected to interact with sites on the protein. The potential mimetics or ligands are then screened for activity and/or binding. For BPI-related mimetics or ligands, screening methods can be selected from assays for at least one biological activity of BPI, *e.g.*, anti-microbial, LPS- binding/neutralizing, heparin binding/neutralizing, and/or anti-thrombotic activities, according to known method steps. Similarly for LBP-, CETP- or PLTP-related mimetics or ligands, such screening methods can be selected from assays for at least one biological activity of LBP, CETP or PLTP, according to known method steps. The resulting mimetics or ligands are then provided by methods of the present invention and are useful for treating, inhibiting or preventing BPI-modulated diseases (or LBP-, CETP- and PLTP-modulated) in animals, including humans.

Thus, as described herein, the present invention provides use of atomic coordinates of a BPI protein, or fragment, analog or variant thereof, to model a BPI protein or a related protein, including a BPI-related lipid transfer protein, such as LBP, CETP or PLTP, or fragment, analog or variant thereof.

The present invention also provides use of atomic coordinates of a BPI protein wherein the BPI protein comprises a binding site characterized by amino acid residues of at least one binding pocket as defined in Table 3, and/or wherein the BPI protein comprises a binding site characterized by at least one amino acid sequence, or variant of the sequence, selected from positions about 17 to about 45, positions about 65 to

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about 99 or positions about 142 to about 169 of BPI, or alternatively, a binding site characterized by at least one amino acid sequence, or variant of the sequence, selected from positions about 36 to about 54, positions about 84 to about 109 or positions about 142 to about 164 of BPI.

The present invention provides use of atomic coordinates of a BPI protein to computationally design a chemical compound for mimicking a BPI protein, or fragment, analog or variant thereof, or a BPI-related lipid transfer protein, or fragment, analog or variant thereof, including, for example, lipopolysaccharide-binding protein (LBP), cholesteryl ester transferase protein (CETP) or phospholipid transfer protein (PLTP), or fragment, analog, or variant thereof.

The present invention also provides use of atomic coordinates of BPI protein to design a chemical compound capable of associating with a BPI-related lipid binding protein, or fragment, analog or variant thereof, including, for example, bactericidal/permeability-increasing protein (BPI), lipopolysaccharide-binding protein (LBP), cholesteryl ester transferase protein (CETP) or phospholipid transfer protein (PLTP), or fragment, analog or variant thereof.

The present invention provides use of atomic coordinates of a BPI protein to design a model of ligands in an active site of a lipid binding protein, including, for example, BPI protein, lipopolysaccharide-binding protein (LBP), cholesteryl ester transferase protein (CETP) or phospholipid transfer protein (PLTP), or fragment, analog or variant thereof.

The present invention provides use of atomic coordinates of a bactericidal/permeability-increasing ("BPI") protein, to design compounds with at least one activity selected from the group consisting of antibacterial, antifungal, antimycobacterial, antichlamydial, antiprotozoan, heparin-binding, endotoxin-binding, heparin-neutralizing, endotoxin-neutralizing, inhibition of tumor and endothelial cell proliferation, inhibition of angiogenesis, anti-inflammatory, anticoagulant and antithrombolytic. The coordinates disclosed herein are suitable for all of the aforementioned uses of atomic coordinates.

The present invention provides a method of three-dimensional modeling of a BPI protein or BPI-related lipid transfer protein comprising the steps of: (a) providing three-dimensional atomic coordinates derived from X-ray diffraction measurements

of a BPI protein in a computer readable format; (b) inputting the data from step (a) into a computer with appropriate software programs; and (c) generating a three-dimensional structural representation of the BPI protein or BPI-related lipid transfer protein suitable for visualization and further computational manipulation; particularly wherein the BPI protein comprises a binding site characterized by amino acid residues of at least one binding pocket as defined in Table 3, or wherein the BPI protein comprises a binding site characterized by at least one amino acid sequence, or variant of the sequence, selected from positions about 17 to about 45, positions about 65 to about 99 or positions about 142 to about 169 of BPI or wherein the BPI protein comprises a binding site characterized by amino acid residues of at least one binding pocket as defined in Table 3 and a binding site characterized by at least one amino acid sequence, or variant of the sequence, selected from positions about 36 to about 54, positions about 84 to about 109 or positions about 142 to about 164 of BPI, or alternatively from about positions 36 to about 54, from about positions 84 to about 109, or about positions 142 to about 164.

The present invention provides a method for providing an atomic model of a BPI protein, BPI-related lipid binding protein, or fragment, analog or variant thereof, comprising (a) providing a computer readable medium having stored thereon atomic coordinate/x-ray diffraction data of a BPI protein, or fragment, analog or variant thereof, in crystalline form, the data sufficient to model the three-dimensional structure of the BPI protein, or fragment, analog or variant thereof; (b) analyzing, on a computer using at least one subroutine executed in said computer, atomic coordinate/x-ray diffraction data from (a) to provide atomic coordinate data output defining an atomic model of said BPI protein, BPI-related binding lipid protein or fragment, analog or variant thereof, said analyzing utilizing at least one computing algorithm selected from the group consisting of data processing and reduction, auto-indexing, intensity scaling, intensity merging, amplitude conversion, truncation, molecular replacement, molecular alignment, molecular refinement, electron density map calculation, electron density modification, electron map visualization, model building, rigid body refinement, positional refinement; and (c) obtaining atomic coordinate data defining the three-dimensional structure of at least one of said BPI protein, BPI-related lipid binding protein, or fragment, analog or variant thereof;

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particularly wherein said computer readable medium further has stored thereon data corresponding to a nucleic acid sequence or an amino acid sequence data comprising at least one structural domain or functional domain of a BPI, LBP, CETP or PLTP corresponding to at least one BPI or mutant primary sequence or fragment, analog or variant thereof; and wherein said analyzing step further comprises analyzing said sequence data.

The present invention provides a computer-based system for providing atomic model data of the three-dimensional structure of a BPI protein, BPI-related lipid binding protein or fragment, analog or variant thereof, comprising the following elements: (a) at least one computer readable medium (CRM) having stored thereon atomic coordinate/x-ray diffraction data of a BPI protein, or fragment, analog or variant thereof; (b) at least one computing subroutine that, when executed in a computer, causes the computer to analyze atomic coordinate/x-ray diffraction data from (a) to provide atomic coordinate data output defining an atomic model of a BPI protein, BPI-related lipid binding protein or fragment, analog or variant thereof, said analyzing utilizing at least one computing subroutine selected from the group consisting of data processing and reduction, auto-indexing, intensity scaling, intensity merging, amplitude conversion, truncation, molecular replacement, molecular alignment, molecular refinement, electron density map calculation, electron density modification, electron map visualization, model building, rigid body refinement, positional refinement; and (c) retrieval means for obtaining atomic coordinate output data substantially defining the three-dimensional structure of said BPI protein, BPI-related lipid binding protein or fragment, analog or variant thereof.

The present invention provides a method for providing a computer atomic model of a ligand of a BPI protein, BPI-related lipid binding protein, or fragment, analog or variant thereof, comprising: (a) providing a computer readable medium (CRM) having stored thereon atomic coordinate data of a BPI protein, or fragment, analog, or variant thereof; (b) providing a CRM having stored thereon atomic coordinate data sufficient to generate atomic models of potential ligands of said BPI protein, BPI-related lipid binding protein, or fragment, analog, or variant thereof; (c) analyzing on a computer, using at least one subroutine executed in said computer, the atomic coordinate data from (a) and ligand data from (b), to determine binding sites

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of BPI protein, BPI-related lipid binding protein, or fragment, analog, or variant thereof, and to provide atomic coordinate data defining an atomic model of at least one ligand of said BPI protein, BPI-related lipid binding protein, or fragment, analog or variant thereof, said analyzing utilizing computing subroutines selected from the group consisting of data processing and reduction, auto-indexing, intensity scaling, intensity merging, amplitude conversion, truncation, molecular replacement, molecular alignment, molecular refinement, electron density map calculation, electron density modification, electron map visualization, model building, rigid body refinement, positional refinement; and (d) obtaining atomic coordinate model output data defining the three-dimensional structure of said at least one ligand of said BPI protein, BPI-related lipid binding protein, or fragment, analog, or variant thereof.

The present invention provides a computer-based system for providing an atomic model of at least one ligand of a BPI protein, BPI-related lipid binding protein, or fragment, analog or variant thereof, comprising the following elements: (a) a computer readable medium (CRM) having stored thereon atomic coordinate data of a BPI protein, fragment, analog or variant thereof; (b) a CRM having stored thereon atomic coordinate data sufficient to generate atomic models of potential ligands of a BPI protein, BPI-related lipid binding protein, or fragment, analog or variant thereof; (c) at least one computing subroutine for analyzing on a computer, the atomic coordinate data from (a) and (b), to determine binding sites of BPI protein, BPI-related lipid binding protein. or fragment, analog, or variant thereof, and to provide data output defining an atomic model of at least one potential ligand of BPI protein, BPI-related lipid binding protein, or fragment, analog, or variant thereof, said analyzing utilizing at least one computing subroutine selected from the group consisting of data processing and reduction, auto-indexing, intensity scaling, intensity merging, amplitude conversion, truncation, molecular replacement, molecular alignment, molecular refinement, electron density map calculation, electron density modification, electron map visualization, model building, rigid body refinement, positional refinement; and (d) retrieval means for obtaining atomic coordinate data of said at least one ligand of a BPI protein, BPI-related lipid binding protein, or fragment, analog or variant thereof.

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said at least one ligand of a BPI protein, BPI-related lipid binding protein, or fragment, analog or variant thereof.

Other objects of the invention will be apparent to one of ordinary skill in the art from the following detailed description and examples relating to the present invention.

Brief Description of the Figures

Fig. 1 (A) A ribbon diagram of residues 1-456 of BPI illustrating its boomerang shape. The NH_2-terminal domain is shown; the COOH-terminal domain and the two phosphatidylcholine molecules are shown. The linker is also shown, and the disulfide bond is shown as a ball-and-stick model. **(B)** View after rotating (A) 70° about the long axis of the molecule. Figure produced with MOLSCRIPT [P. Krauliz, *J. Appl. Cryst., 24*:926 (1991)] and RASTER3D [E. A. Merrit and M. E. P. Murphy, *Acta Crystallogr., D50*:889 (1994); D. J. Bacon and W. F. Anderson, *J. Mo. Graphics, 6*:219 (1988)].

Fig. 2 (A) Schematic drawing of the novel BPI domain fold, shown in same orientation as the NH_2-terminal domain in Fig. 1B **(B)** Superposition of the NH_2- and COOH-terminal domains of BPI showing the overall topological similarity. Residues 1 to 230 and 250 to 456 are shown. The NH_2-terminal domain is in the same orientation as Fig. 1A.

Fig. 3 Electron density of the final 2.8 Å MIR map contoured at 1.0 σ and superimposed on the refined model. The area shown is in the lipid binding pocket of the NH_2-terminal domain of BPI. The phosphatidylcholine and the surrounding protein atoms are shown.

Fig. 4 (A) The covalent structure of phosphatidylcholine and the lipid A region of LPS from *E. coli and S. typhimurium*. Phosphate groups are indicated by P. Adapted with changes from [C. R. H. Raetz, *Annu. Rev. Biochem, 59*:129 (1990)]. **(B)** Slice through the interior of BPI showing the lipid binding pocket in the NH_2-terminal domain. The solvent accessible surface of the protein was calculated without lipid present, the interior of the protein and the phosphatidylcholine are shown. Protein residues are shown as ball-and-stick.

Figure produced with MSP [M. L. Connolly, *Science, 221*:709 (1983); M. L. Connolly, *J. Am. Chem. Soc., 107*:1118 (1985)].

Figs. 5 (A) and 5 (B) The amino acid sequences of human BPI, LBP, PLTP, and CETP. The alignment was performed with CLUSTAL [D. G. Higgins and P. M. Sharp, *Gene, 73*:237 (1989)] using all eleven known protein sequences from mammals [R. R. Schuman, et al., *Science, 249*:1429 (1990); D. Drayna et al., *Nature, 327*:632 (1987); R. Day et al., *J. Biol. Chem., 269*:9388 (1994); S.R. Leong and T. Camerato, *Nucleic Acids Res., 18*:3052 (1990); M. Nagashima, J. W. McLean, R. M. Lawn, *J. Lipid Res., 29*:1643 (1988); M. E. Pape, E. F. Rehber, K. R. Marotti, G. W. Melchior, *Artheriosclerosis 11*:1759 (1991); G. Su et al., *J. Immunol., 153*:743 (1994); P. W. Gray et al., *J. Biol. Chem. 264*: 9505 (1989); Albers et al., *Biochem. Biophys. Acta, 1258*:27 (1995); X. C. Jiang et al., *Biochemistry, 34*:7258 (1995); L. B. Agellon et al., *Biochemistry, 29*:1372 (1990); X. C. Jiang et al., *J. Biol. Chem., 266*:4631 (1991)] but only the four human sequences are shown. Residues that are completely conserved in all proteins are indicated below the sequence *; those which are highly conserved are indicated by •. The secondary structure of BPI is indicated above the sequences. The β strands are indicated by arrows; strands which make up the central β sheet are shown with gray arrows. Because of the β bulges and pronounced twisting, some of the β strands have one or more residues that do not show classical H-bonding patterns or $\Phi\Psi$ angles; these breaks are indicated by ^ above the strands. The α helices are shown as cylinders, and one-residue breaks in helices B and B′ are indicated with a vertical dashed line. The horizontal dashed line indicates the linker region. Peptides from BPI and LBP with the highest LPS-binding activity (Little, et al., *J. Biol. Chem.* 268: 1865 (1994); Taylor et al., *J. Biol. Chem. 270*: 17934 (1995)) are in bold italics. The disulfide bond is indicated by S-S. Residues with atoms within 4 Å of the NH_2-terminal lipid are highlighted with gray shading; residues within 4 Å of the COOH-terminal lipid are shown with white letters in black boxes.

Fig. 6 Block diagram of a computer system 102 that can be used to implement the present invention. The computer system 102 includes a processor 106 connected to

a bus 104. Also connected to the bus 104 are a main memory 108 (preferably implemented as random access memory, RAM) and a variety of secondary storage memory 110, such as a hard drive 112, a removable medium storage device 114, a command device 118, and a visualization device, 120. Also included is a removable storage medium 116.

Detailed Description

The present invention provides methods for crystallizing a BPI protein product where the crystals diffract x-rays with sufficiently high resolution to allow determination of the three-dimensional structure of the BPI protein product, including atomic coordinates. The three-dimensional structure (e.g, as provided on computer readable media as described herein) is useful for rational drug design of BPI-related (and LBP-, CETP-, PLTP-related) mimetics and/or ligands. Specifically provided is a method for crystallizing a recombinant non-glycosylated human BPI analog holoprotein comprising a 456 amino acid sequence wherein the amino acid serine at position 351 has been changed to alanine. The three-dimensional structure is useful for modeling and/or synthesizing BPI-related mimetics or ligands. Such BPI-related mimetics or ligands are useful for treating, inhibiting or preventing BPI-modulated diseases.

The present invention thus includes methods of expressing, purifying and crystallizing a BPI protein product from suitable sources, such as eukaryotic cells or tissues. The present invention also provides crystallized BPI protein products by these methods. The crystallized BPI is analyzed by x-ray diffraction techniques to obtain high resolution diffraction patterns and atomic coordinates that are suitable for molecular modeling.

As used herein, "BPI protein product" or "BPI protein" includes naturally and recombinantly produced BPI protein; natural, synthetic, and recombinant biologically active polypeptide fragments of BPI protein; biologically active polypeptide variants of BPI protein or fragments thereof, including hybrid fusion proteins and dimers; biologically active polypeptide analogs of BPI protein or fragments or variants thereof, including cysteine-substituted analogs; and BPI-derived peptides. The BPI protein products for therapeutic or diagnostic uses may be generated and/or isolated by any means known in the art. U.S. Patent No. 5,198,541, the disclosure of which

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is incorporated herein by reference, discloses recombinant genes encoding and methods for expression of BPI proteins including recombinant BPI holoprotein, referred to as rBPI (also referred to as $rBPI_{55}$ or simply $rBPI_{50}$) and recombinant fragments of BPI. U.S. Patent Application Ser. No. 07/885,501, now abandoned, and a continuation-in-part thereof, U.S. Patent Application Ser. No. 08/072,063, filed May 19, 1993, issued as U.S. Patent 5,439,807 on August 8, 1995 and corresponding PCT Application No. 93/04752 filed May 19, 1993, which are all incorporated herein by reference, disclose novel methods for the purification of recombinant BPI protein products expressed in and secreted from genetically transformed mammalian host cells in culture and discloses how one may produce large quantities of recombinant BPI products suitable for incorporation into stable, homogeneous pharmaceutical preparations.

Biologically active fragments of BPI (BPI fragments) include biologically active molecules that have the same or similar amino acid sequence as a natural human BPI holoprotein, except that the fragment molecule lacks amino-terminal amino acids, internal amino acids, and/or carboxy-terminal amino acids of the holoprotein. Nonlimiting examples of such fragments include a N-terminal fragment of natural human BPI of approximately 25 kD, described in Ooi et al., *J. Exp. Med.*, *174*:649 (1991), and the recombinant expression product of DNA encoding N-terminal amino acids from 1 to about 193 or 199 of natural human BPI, described in Gazzano-Santoro et al., *Infect. Immun. 60*:4754-4761 (1992), and referred to as $rBPI_{23}$. In that publication, an expression vector was used as a source of DNA encoding a recombinant expression product ($rBPI_{23}$) having the 31-residue signal sequence and the first 199 amino acids of the N-terminus of the mature human BPI, as set out in Figure 1 of Gray et al., *supra*, except that valine at position 151 is specified by GTG rather than GTC and residue 185 is glutamic acid (specified by GAG) rather than lysine (specified by AAG). Recombinant holoprotein (rBPI) has also been produced having the sequence (SEQ ID NOS: 1 and 2) set out in Figure 1 of Gray et al., *supra*, with the exceptions noted for $rBPI_{23}$ and with the exception that residue 417 is alanine (specified by GCT) rather than valine (specified by GTT). Other examples include dimeric forms of BPI fragments, as described in U.S. Patent No. 5,447,913, and corresponding PCT Application No. PCT/US95/03125, the

disclosures of which are incorporated herein by reference. Preferred dimeric products include dimeric BPI protein products wherein the monomers are amino-terminal BPI fragments having the N-terminal residues from about 1 to 175 to about 1 to 199 of BPI holoprotein. A particularly preferred dimeric product is the dimeric form of the BPI fragment having N-terminal residues 1 through 193, designated $rBPI_{42}$ dimer.

Biologically active variants of BPI (BPI variants) include but are not limited to recombinant hybrid fusion proteins, comprising BPI holoprotein or biologically active fragment thereof and at least a portion of at least one other polypeptide, and dimeric forms of BPI variants. Examples of such hybrid fusion proteins and dimeric forms are described by Theofan et al. in U.S. Patent Application Serial No. 07/885,911, now abandoned, and a continuation-in-part application thereof, U.S. Patent Application Serial No. 08/064,693 filed May 19, 1993, issued as U.S. Patent 5,643,570 on July 1, 1997 and corresponding PCT Application No. US93/04754 filed May 19, 1993, which are all incorporated herein by reference and include hybrid fusion proteins comprising, at the amino-terminal end, a BPI protein or a biologically active fragment thereof and, at the carboxy-terminal end, at least one constant domain of an immunoglobulin heavy chain or allelic variant thereof. Similarly configured hybrid fusion proteins involving part or all Lipopolysaccharide Binding Protein (LBP) are also contemplated for use in the present invention.

Biologically active analogs of BPI (BPI analogs) include but are not limited to BPI protein products wherein one or more amino acid residues have been replaced by a different amino acid. For example, U.S. Patent No. 5,420,019 and corresponding PCT Application No. US94/01235, filed February 2, 1994, the disclosures of which are incorporated herein by reference, discloses polypeptide analogs of BPI and BPI fragments wherein a cysteine residue is replaced by a different amino acid. A preferred BPI protein product described by this application is the expression product of DNA encoding from amino acid 1 to approximately 193 or 199 of the N-terminal amino acids of BPI holoprotein, but wherein the cysteine at residue number 132 is substituted with alanine and is designated $rBPI_{21}\Delta cys$ or $rBPI_{21}$. Other examples include dimeric forms of BPI analogs; e.g. U.S. Patent Application Serial No. 08/212,132 filed March 11, 1994, issued as U.S. Patent 5,447,913 on

September 5, 1995 and corresponding PCT Application No. PCT/US95/03125, the disclosures of which are incorporated herein by reference.

Other BPI protein products useful according to the methods of the invention are peptides derived from or based on BPI produced by recombinant or synthetic means (BPI-derived peptides), such as those described in U.S. Patent Application Serial No. 08/504,841 filed July 20, 1995 and in PCT Application No. PCT/US94/10427 filed September 15, 1994, which corresponds to U.S. Patent Application Serial No. 08/306,473 filed September 15, 1994, issued as U.S. Patent 5,652,332 on July 29, 1997, and PCT Application No. US94/02465 filed March 11, 1994, which corresponds to U.S. Patent Application Serial No. 08/209,762, filed March 11, 1994, issued as U.S. Patent 5,733,872 on March 31, 1998, which is a continuation-in-part of U.S. Patent Application Serial No. 08/183,222, filed January 14, 1994, now abandoned, which is a continuation-in-part of U.S. Patent Application Ser. No. 08/093,202 filed July 15, 1993, now abandoned, (for which the corresponding international application is PCT Application No. US94/02401 filed March 11, 1994), which is a continuation-in-part of U.S. Patent Application Ser. No. 08/030,644 filed March 12, 1993, issued as U.S. Patent 5,348,942 on September 20, 1994, the disclosures of all of which are incorporated herein by reference.

Presently preferred BPI protein products include recombinantly-produced N-terminal fragments of BPI, especially those having a molecular weight of approximately between 21 to 25 kD such as $rBPI_{23}$ or $rBPI_{21}$, or dimeric forms of these N-terminal fragments (e.g., $rBPI_{42}$ dimer). Additionally, preferred BPI protein products include $rBPI_{50}$ and BPI-derived peptides.

The administration of BPI protein products is preferably accomplished with a pharmaceutical composition comprising a BPI protein product and a pharmaceutically acceptable diluent, adjuvant, or carrier. The BPI protein product may be administered without or in conjunction with known surfactants, other chemotherapeutic agents or additional known anti-microbial agents. One pharmaceutical composition containing BPI protein products (e.g., $rBPI_{50}$, $rRBPI_{23}$) comprises the BPI protein product at a concentration of 1 mg/ml in citrate buffered

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saline (5 or 20 mM citrate, 150 mM NaCl, pH 5.0) comprising 0.1% by weight of poloxamer 188 (Pluronic F-68, BASF Wyandotte, Parsippany, NJ) and 0.002% by weight of polysorbate 80 (Tween 80, ICI Americas Inc., Wilmington, DE). Another pharmaceutical composition containing BPI protein products (e.g., $rBPI_{21}$) comprises the BPI protein product at a concentration of 2 mg/mL in 5 mM citrate, 150 mM NaCl, 0.2% poloxamer 188 and 0.002% polysorbate 80. Such combinations are described in PCT Application No. US94/01239 filed February 2, 1994, which corresponds to U.S. Patent Application Ser. No. 08/190,869 filed February 2, 1994, issued as U.S. Patent 5,488,034 on January 30, 1996, and U.S. Patent Application Ser. No. 08/012,360 filed February 2, 1993, now abandoned, the disclosures of all of which are incorporated herein by reference. Additional formulations are provided in U.S. Patent Application Ser. Nos. 08/372,104, filed January 13, 1995, now abandoned, 08/530,599, filed September 19, 1995, now abandoned, and 08/586,133, filed January 12, 1996 and corresponding WO96/21436 (PCT/US96/01095).

The x-ray diffraction patterns of the invention are now discovered to be of sufficiently high resolution to be useful for three-dimensional modeling of a BPI. Preferably the resolution is in the range of 1.5 to 3.5 Å, preferably 1.5-3.0 Å and more preferably $\leq$ 2.6 Å.

Three-dimensional modeling is performed using the diffraction coordinates from these x-ray diffraction patterns. The coordinates are entered into one or more computer programs for molecular modeling, as known in the art. Such molecular modeling can utilize known x-ray diffraction molecular modeling algorithms or molecular modeling software to generate atomic coordinates corresponding to the three-dimensional structure of at least one BPI or a fragment thereof.

The entry of the coordinates of the x-ray diffraction patterns and the amino acid sequence into such programs results in the calculation of most probable secondary, tertiary and quaternary structures of the protein, including overall atomic coordinates of a BPI or a fragment thereof. These structures are combined and refined by additional calculations using such programs to determine the probable or actual three-dimensional structure of the BPI, including potential or actual active or binding sites of the protein.

Such molecular modeling (and related) programs useful for rational drug design of ligands or mimetics, are also provided by the present invention. The drug design uses computer modeling programs which calculate how different molecules interact with the various sites of the BPI. This procedure determines potential ligands or mimetics of a BPI or at least one fragment thereof. The actual BPI-ligand complexes or mimetics are crystallized and analyzed using x-ray diffraction. The diffraction pattern coordinates are similarly used to calculate the three-dimensional interaction of a ligand and the BPI or a mimetic, in order to confirm that the ligand binds to, or changes the conformation of, a particular site on the BPI, or where the mimetic has a similar three-dimensional structure to that of a BPI or a fragment thereof.

The potential ligands or mimetics are then screened for activity relating to a BPI. Such screening methods are selected from assays for at least one biological activity of the native BPI.

The resulting ligands or mimetics, provided by methods of the present invention, are useful for treating, screening or preventing bacterial infections in animals, such as mammals (including humans) and birds. Mimetics or ligands of a particular BPI will similarly react with other BPIs from other species, subgenera or genera of the BPI source organism.

Also provided are biologically active BPI proteins. A BPI protein is also provided as a crystallized protein suitable for x-ray diffraction analysis. The x-ray diffraction patterns obtained by the x-ray analysis are of moderately high to high resolution, *e.g.*, 1.5-3.5 Å. The coordinates from these diffraction patterns are suitable and useful for three-dimensional modeling of the crystallized protein.

During the three-dimensional modeling of the BPI, these coordinates are entered with the BPI amino acid sequence into computer modeling programs to generate secondary, tertiary and quaternary structures of the BPI, as atomic coordinates. These structures together provide the three-dimensional structure of the BPI. The calculated and confirmed three-dimensional structure is then used for rational drug design of ligands or mimetics of the BPI or a fragment thereof.

The determination of the three-dimensional structure of a BPI protein thus has a broad-based utility. Significant sequence identity and conservation of important

structural elements is expected to exist among the BPI proteins of a particular species, subgenus, genus, or family. Therefore, the three-dimensional structure from one or a few BPI proteins can be used to identify therapeutics with one or more of the biological activities of BPI (and/or those of related proteins such as LBP, CETP and PLTP).

Determination of Protein Structures

Different techniques give different and complementary information about protein structure. The primary structure is obtained by biochemical methods, either by direct determination of the amino acid sequence from the protein, or from the nucleotide sequence of the corresponding gene or cDNA. The quaternary structure of large proteins or aggregates can also be determined by electron microscopy. To obtain the secondary and tertiary structure, which requires detailed information about the arrangement of atoms within a protein, x-ray crystallography is preferred.

The first prerequisite for solving the three-dimensional structure of a protein by x-ray crystallography is a well-ordered crystal that will diffract x-rays strongly. The crystallographic method directs a beam of x-rays onto a regular, repeating array of many identical molecules so that the x-rays are diffracted from it in a pattern from which the structure of an individual molecule can be retrieved. Well-ordered crystals of globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and crystals thereof contain large holes or channels that are formed between the individual molecules. These channels, which usually occupy more than half the volume of the crystal, are filled with disordered solvent molecules. The protein molecules are in contact with each other at only a few small regions. This is one reason why structures of proteins determined by x-ray crystallography are generally the same as those for the proteins in solution.

The formation of crystals is dependent on a number of different parameters, including pH, temperature, protein, concentration, the nature of the solvent and precipitant, as well as the presence of added ions or ligands to the protein. Many routine crystallization experiments may be needed to screen all these parameters for the few combinations that might give crystal suitable for x-ray diffraction analysis. Crystallization robots can automate and speed up the work of reproducibly setting up large number of crystallization experiments.

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A pure and homogeneous protein sample is important for successful crystallization. Proteins obtained from cloned genes in efficient expression vectors can be purified quickly to homogeneity in large quantities in a few purification steps. A protein to be crystallized is preferably at least 93-99% pure according to standard criteria of homogeneity. Crystals form when molecules are precipitated very slowly from supersaturated solutions. The most frequently used procedure for making protein crystals is the hanging-drop method, in which a drop of protein solution is brought very gradually to supersaturation by loss of water from the droplet to the larger reservoir that contains salt or polyethylene glycol solution.

Different crystal forms can be more or less well-ordered and hence give diffraction patterns of different quality. As a general rule, the more closely the protein molecules pack, and consequently the less water the crystals contain, the better is the diffraction pattern because the molecules are better ordered in the crystal.

X-rays are electromagnetic radiation at short wavelengths, emitted when electrons jump from a higher to a lower energy state. In conventional sources in the laboratory, x-rays are produced by high-voltage tubes in which a metal plate, the anode, is bombarded with accelerating electrons and thereby caused to emit x-rays of a specific wavelength, so-called monochromatic x-rays. The high voltage rapidly heats up the metal plate, which therefore has to be cooled. Efficient cooling is achieved by so-called rotating anode x-ray generators, where the metal plate revolves during the experiment so that different parts are heated up.

More powerful x-ray beams can be produced in synchrotron storage rings where electrons (or positrons) travel close to the speed of light. These particles emit very strong radiation at all wavelengths from short gamma rays to visible light. When used as an x-ray source, only radiation within a window of suitable wavelengths is channeled from the storage ring. Polychromatic x-ray beams are produced by having a broad window that allows through x-ray radiation with wavelengths of 0.2-3.5Å.

In diffraction experiments a narrow and parallel beam of x-rays is taken out from the x-ray source and directed onto the crystal to produce diffracted beams. The incident primary beam causes damage to both protein and solvent molecules. The crystal is, therefore, usually cooled to prolong its lifetime (*e.g.*,-220 to -50°C). The

primary beam must strike the crystal from many different directions to produce all possible diffraction spots, and so the crystal is rotated in the beam during the experiment.

The diffracted spots are recorded either on a film, the classical method, or by an electronic detector. The exposed film has to be measured and digitized by a scanning device, whereas electronic detectors feed the signals they detect directly in a digitized form into a computer. Electronic area detectors (an electronic film) significantly reduce the time required to collect and measure diffraction data.

When the primary beam from an x-ray source strikes the crystal, some of the x-rays interact with the electrons on each atom and cause them to oscillate. The oscillating electrons serve as a new source of x-rays, which are emitted in almost all directions, referred to as scattering. When atoms (and hence their electrons) are arranged in a regular three-dimensional array, as in a crystal, the x-rays emitted from the oscillating electrons interfere with one another. In most cases, these x-rays, colliding from different directions, cancel each other out; those from certain directions, however, will add together to produce diffracted beams of radiation that can be recorded as a pattern on a photographic plate or detector.

The diffraction pattern obtained in an x-ray experiment is related to the crystal that caused the diffraction. X-rays that are reflected from adjacent planes travel different distances, and diffraction only occurs when the difference in distance is equal to the wavelength of the x-ray beam. This distance is dependent on the reflection angle, which is equal to the angle between the primary beam and the planes.

The relationship between the reflection angle (Θ), the distance between the planes (d), and the wavelength (λ) is given by Bragg's law: $2d \sin \Theta = \lambda$. This relation can be used to determine the size of the unit cell in the crystal. Briefly, the position on the film of the diffraction data relates each spot to a specific set of planes through the crystal. By using Bragg's law, these positions can be used to determine the size of the unit call.

Each atom in a crystal scatters x-rays in all directions, and only those that positively interfere with one another, according to Bragg's law, give rise to diffracted beams that can be recorded as a distinct diffraction spot above background. Each

diffraction spot is the result of interference of all x-rays with the same diffraction angle emerging from all atoms. For example, for the protein crystal of myoglobin, each of the about 20,000 diffracted beams that have been measured contain scattered x-rays from each of the around 1500 atoms in the molecule. To extract information about individual atoms from such a system requires considerable computation. The mathematical tool that is used to handle such problems is called the Fourier transform.

Each diffracted beam, which is recorded as a spot on the film, is defined by three properties: the amplitude, which we can measure from the intensity of the spot; the wavelength, which is set by the x-ray source; and the phase, which is lost in x-ray experiments. All three properties are needed for all of the diffracted beams, in order to determine the position of the atoms giving rise to the diffracted beams.

For larger molecules, protein crystallographers have determined the phases in many cases using a method called multiple isomorphous replacement (MIR) (including heavy metal scattering), which requires the introduction of new x-ray scatterers into the unit cell of the crystal. These additions are usually heavy atoms (so that they make a significant contribution to the diffraction pattern), such that there should not be too many of them (so that their positions can be located); and they should not change the structure of the molecule or of the crystal cell, *i.e.*, the crystals should be isomorphous. Isomorphous replacement is usually done by diffusing different heavy-metal complexes into the channels of the preformed protein crystals. The protein molecules expose side chains (such as SH groups) into these solvent channels that are able to bind heavy metals. It is also possible to replace endogenous light metals in metalloproteins with heavier ones, *e.g.*, zinc by mercury, or calcium by samarium.

Since such heavy metals contain many more electrons than the light atoms (H,N,C,O and S) of the protein, they scatter x-rays more strongly. All diffracted beams would therefore increase in intensity after heavy-metal substitution if all interference were positive. In fact, however, some interference is negative; consequently, following heavy-metal substitution, some spots measurably increase in intensity, others decrease, and many show no detectable difference.

Phase differences between diffracted spots can be determined from intensity changes following heavy-metal substitution. First, the intensity differences are used

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to deduce the positions of the heavy atoms in the crystal unit cell. Fourier summations of these intensity differences give maps of the vectors between the heavy atoms, the so-called Patterson maps. From these vector maps the atomic arrangement of the heavy atoms is deduced. From the positions of the heavy metals in the unit cell, one can calculate the amplitudes and phases of their contribution to the diffracted beams of protein crystals containing heavy metals.

This knowledge is then used to find the phase of the contribution from the protein in the absence of the heavy-metal atoms. As both the phase and amplitude of the heavy metals and the amplitude of the protein alone is known, as well as the amplitude of the protein plus heavy metals (*i.e.*, protein heavy-metal complex), one phase and three amplitudes are known. From this, the interference of the x-rays scattered by the heavy metals and protein can be calculated to see if it is constructive or destructive. The extent of positive or negative interference, with knowledge of the phase of the heavy metal, given an estimate of the phase of the protein. Because two different phase angles are determined and are equally good solutions, a second heavy-metal complex can be used which also gives two possible phase angles. Only one of these will have the same value as one of the two previous phase angles; it therefore represents the correct phase angle. In practice, more than two different heavy-metal complexes are usually made in order to give a reasonably good phase determination for all reflections. Each individual phase estimate contains experimental errors arising from errors in the measured amplitudes. Furthermore, for many reflections, the intensity differences are too small to measure after one particular isomorphous replacement, and others can be tried.

The amplitudes and the phases of the diffraction data from the protein crystals are used to calculate an electron-density map of the repeating unit of the crystal. This map then has to be interpreted as a polypeptide chain with a particular amino acid sequence. The interpretation of the electron-density map is made more complex by several limitations of the data. First of all, the map itself contains errors, mainly due to errors in the phase angles. In addition, the quality of the map depends on the resolution of the diffraction data, which in turn depends on how well-ordered the crystals are. This directly influences the image that can be produced. The resolution

is measured in Å units; the smaller this number is, the higher the resolution and therefore the greater the amount of detail that can be seen.

Building the initial model is a trial-and-error process. First, one has to decide how the polypeptide chain weaves its way through the electron-density map. The resulting chain trace constitutes a hypothesis, by which one tries to match the density of the side chains to the known sequence of the polypeptide. When a reasonable chain trace has finally been obtained, an initial model is built to give the best fit of the atoms to the electron density. Computer graphics are used both for chain tracing and for model building to present the data and manipulated the models.

The initial model will contain some errors. Provided the protein crystals diffract to high enough resolution (*e.g.*, better than 3.5 Å), most or substantially all of the errors can be removed by crystallographic refinement of the model using computer algorithms. In this process, the model is changed to minimize the difference between the experimentally observed diffraction amplitudes and those calculated for a hypothetical crystal containing the model (instead of the real molecule). This difference is expressed as an R factor (residual disagreement) which is 0.0 for exact agreement and about 0.59 for total disagreement.

In general, the R factor is preferably between 0.15 and 0.35 (such as less than about 0.24-0.28) for a well-determined protein structure. The residual difference is a consequence of errors and imperfections in the data. These derive from various sources, including slight variations in the conformation of the protein molecules, as well as inaccurate corrections both for the presence of solvent and for differences in the orientation of the microcrystals from which the crystal is built. This means that the final model represents an average of molecules that are slightly different both in conformation and orientation.

In refined structures at high resolution, there are usually no major errors in the orientation of individual residues, and the estimated errors in atomic positions are usually around 0.1-0.2 Å, provided the amino acid sequence is known. Hydrogen bonds, both within the protein and to bound ligands, can be identified with a high degree of confidence.

Those of skill in the art understand that a set of structure coordinates determined by X-ray crystallography is not without standard error. For the purpose

of this invention, any set of structure coordinates for BPI-protein that have a root mean square deviation of protein backbone atoms (N, Cα, C and O) of less that 0.75Å when superimposed -- using backbone atoms -- on the structure coordinates listed in Table 4 shall be considered identical.

Most x-ray structures are determined to a resolution between 1.7 Å and 3.5 Å. Electron-density maps with this resolution range are preferably interpreted by fitting the known amino acid sequences into regions of electron density in which individual atoms are not resolved.

An amino acid sequence is preferred for accurate x-ray structure determination. Thus, recombinant DNA techniques have had a double impact on x-ray structural work. When a protein is cloned and overexpressed for structural studies, the amino acid sequence, necessary for the x-ray work, is also quickly obtained via the nucleotide sequence. Recombinant DNA techniques give us not only abundant supplies of rare proteins, but also their amino acid sequence as a bonus.

Overview of BPI Purification and Crystallization Methods

In general, a BPI protein is purified as described in Example 1. The resulting BPI is in sufficient purity and concentration for crystallization. The BPI is then isolated and assayed for biological activity and for lack of aggregation (which interferes with crystallization). The purified BPI preferably runs as a single band under reducing or nonreducing polyacrylamide gel electrophoresis (PAGE) (nonreducing is used to evaluate the presence of cysteine bridges).

The purified BPI is preferably crystallized using the hanging drop method under varying conditions of at least one of the following: pH, buffer type, buffer concentration, salt type, polymer type, polymer concentration, other precipitating agents and concentration of purified and cleaved BPI. See, *e.g.*, the methods provided in a commercial kit, such as CRYSTAL SCREEN (Hampton Research, Riverside, CA). Differently sized and shaped crystals are tested for suitability for x-ray diffraction. Generally, larger crystals provide better crystallography than smaller crystals, and thicker crystals provide better diffraction than thinner crystals.

Purified BPIs

The results of the purification are optionally analyzed by polyacrylamide gel electrophoresis (PAGE) under reducing or non-reducing conditions. A single band

is preferably obtained. With disulfide-containing BPIs, it is preferred that the analysis of the cleaved BPI be under non-reducing conditions to indicate whether the cleaved protein formed disulfide linked dimers. The amino acid sequence can also be determined according to known methods, or otherwise obtained, as this sequence is important in determining the three-dimensional structure of the cleaved protein (in combination with crystallographic analysis), as described herein, using molecular modeling techniques.

Before crystallization, the purified protein is tested for one or more of the known biological activities of a BPI protein.

It is preferred that the biological activity exceed the activity of the native protein. The preferred result indicates that the BPI protein retains its native structure, which is important for determining the three-dimensional crystal structure of the biologically active molecule. To identify the protease cleavage site, the purified and cleaved protein can be sequenced using known techniques. *See, e.g.*, Murti *et al.*, *Proc. Natl. Acad. Sci. USA 90*:1523-1525 (1993); Takimoto *et al.* (1992), *infra*, entirely incorporated herein by reference.

Protein Crystallization Methods

The hanging drop method is preferably used to crystallize the purified protein. *See, e.g.*, Taylor *et al.*, *J. Mol. Biol. 226*:1287-1290 (1992); Takimoto *et al.* (1992), *infra*; CRYSTAL SCREEN, Hampton Research.

A mixture of the purified protein and precipitant can include the following:

- pH (*e.g.*, 4-9);
- buffer type (*e.g.*, phosphate, cacodylate, acetates, imidazole, Tris HCl, sodium HEPES);
- buffer concentration (*e.g.*, 10-200 mM);
- salt type (*e.g.*, calcium chloride, sodium citrate, magnesium chloride, ammonium acetate, ammonium sulfate, potassium phosphate, magnesium acetate, zinc acetate; calcium acetate)
- polymer type and concentration: (*e.g.*, polyethylene glycol (PEG) 1-50%, average molecular weight 200-10,000);

- other precipitating agents (salts: K, Na tartrate, NH_4SO_4, NaAc, $LiSO_4$, NaFormate, NaCitrate, MgFormate, $NaPO_4$, KPO_4 NH_4PO_4; organics: 2-propanol; non-volatile: 2-methyl-2,4-pentanediol); and
- concentration of purified BPI (*e.g.*, 1.0-100 mg/ml).

See, e.g., CRYSTAL SCREEN, Hampton Research.

A non-limiting example of such crystallization conditions is the following:

- purified protein (*e.g.*, approximately 3-4 mg/ml);
- H_2O;
- precipitant 10-14% Polyethylene glycol (PEG) 8000 buffered with 100 mM cacodylate buffer and 200 mM of Mg acetate;
- at an overall pH of about 3.5-8.5.

The above mixtures are used and screened by varying at least one of pH, buffer type; buffer concentration, precipitating salt type or concentration, PEG type, PEG concentration, and protein concentration. Crystals ranging in size from 0.2-0.7 mm are formed in 1 -7 days. These crystals diffract x-rays to at least 3.5 Å resolution, such as 1.5 -3.5 Å, or any range of value therein, such as 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3.0, with 3.0 Å or less being preferred.

Protein Crystals

Crystals appear after 1-4 days and grow to maximal size within a week. From one ten crystals are observed in one drop and crystal forms can occur, such as, but not limited to, bipyramidal, rhomboid, and cubic. Initial x-ray analyses indicate that such crystals diffract at moderately high to high resolution. When fewer crystals are produced in a drop, they can be much larger size, *e.g.*, 0.4-0.9 mm.

X-ray Crystallography Methods and Molecular Modeling

The crystals so produced for BPI are x-ray analyzed using a suitable x-ray source. Diffraction patterns are obtained. Crystals are preferably stable for at least 10 hrs in the x-ray beam. Frozen crystals (*e.g.*, -220 to -50°C) could also be used for longer x-ray exposures (*e.g.*, 24-72 hrs), the crystals being relatively more stable to the x-rays in the frozen state. To collect the maximum number of useful reflections, multiple frames are optionally collected as the crystal is rotated in the x-ray beam, *e.g.*, for 24-72 hrs. Larger crystals (>0.2 mm) are preferred, to increase

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the resolution of the x-ray diffraction. Alternatively, crystals may be analyzed using a synchrotron high energy x-ray source. Using frozen crystals, x-ray diffraction data is collected on crystals that diffract to a relatively high resolution of 3.5 Å or less, sufficient to solve the three-dimensional structure of BPI in considerable detail, as presented herein.

Native and/or derivative x-ray diffraction data with medium resolution is collected on area detectors mounted on rotating anode x-ray sources. The alternative program DENZO is preferably used for data processing and reduction (Sawyer *et al.*, eds., *Proceedings of CCP4 Study Weekend*, pp. 56-62, SERC Darsbary Lab., UK (1993)).

The resolution is optionally improved using larger crystals, *e.g.*, 0.2mm, making data collection more efficient, particularly for the determination of suitable heavy metal derivatives, such as Hg, Pt, Pb, Ba, Cd, and/or La derivatives.

The heavy metal derivatives are used to determine the phase, *e.g.*, by the isomorphous replacement method. Heavy atom isomorphous derivatives of BPI are used for x-ray crystallography, where the structure is solved using one or several derivatives, which, (when combined) improves the overall figure of merit. Derivatives are identified through Patterson maps and/or cross-phase difference Fourier maps, *e.g.*, using the CCP4 package (SERC Collaborative Computing Project No. 4, Daresbury Laboratory, UK, 1979).

Phases were also obtained or improved by optimization of the anomalous dispersion component of the x-ray scattering which can break the phase ambiguity which a single heavy atom derivative gives. In certain cases phase information may be obtained without the need of a native set of data, through the use of multiple wavelength with anomalous dispersion phasing (MAD phasing). The wavelength of the x-rays used may be selected at a synchrotron source to optimize this anomalous scattering. In this case data from a derivatised crystal or crystals is collected at typically three wavelengths, two of which are very close to the absorption edge of the heavy atom scatterer. One way of obtaining a suitable heavy atom derivatised crystal is to derivatise a known ligand of the protein.

The program MLPHARE (Wolf *et al.*, eds., *Isomorphous Replacement and Anomalous Scattering: Proceedings of CCP4 Study Weekend*, pp. 80-86, SERC

Daresbury Lab., UK (1991)) is optionally used for refinement of the heavy atom parameters and the phases derived from them by comparing at least one of completeness (%), resolution (Å), R^r (%), heavy atom concentration (mM), soaking time, heavy atom sites, phasing power (acentric, centric) (*See* Table 1 as an analogous example from The Crystal Structure of diphtheria toxin, Choe et al., *Nature 357*: 216-222 (1992). Addition of heavy atom derivatives produce an MIR map with recognizable features.

The initial phases are calculated to 3.2 Å, and then improved and extended to a higher resolution of 2.8 Å (*e.g.*, ≤3.0 Å) using solvent flattening, histogram matching and/or Sayre's equation in the program DM (Cowtan and Main, *Acta Crystallogr. D 49*:148-157 (1993)). The skeletonization of DM procedure is optionally used to improve connectivity in the bulk of the protein envelope. Both the MIR and density modified maps are optionally used in subsequent stages, to provide sufficient resolution and/or modeling of surface structures.

Skeletonized representations of electron density maps are then computed. These maps are automatically or manually edited using suitable software, *e.g.*, the graphics package FRODO (Jones *et al.* (1991), *infra*) to give a continuous Cα trace. The BPI sequence is then aligned to the trace. Initially pieces of idealized polypeptide backbone were placed into regions of the electron density map with obvious secondary structures (e.g., α-helix, β-sheet). After a polyalanine model was constructed for the protein, amino acid sidechains were added where density was present in the maps. The amino acid sequence of BPI was then examined for regions with distinct sidechain patterns (e.g., three consecutive aromatic rings). When a pattern in the sequence was found to match an area of the map, the correct sidechains were built onto the existing model. Eventually fragments containing recognizable sequence motifs were connected into a single chain, completing the tracing of the amino acid sequence into the maps.

X-ray diffraction data (*e.g.*, to ≤3.0 Å) was collected on an RAXIS 11C area detector (*e.g.*, a Mar imaging plate) mounted on a RIGAKU rotating anode or alternatively a synchrotron x-ray source, and processed using a suitable oscillation data reduction program (DENZO, Sawyer *et al.* eds., *Proceedings of CCP4 Study Weekend*, pp. 56-62, SERC Darsbary Lab., UK (1993). Cycles of simulated

annealing against these data were refined using the program X-PLOR for molecular dynamics for R-factor refinement (X-PLOR, Brünger *et al.*, *J. Mol. Biol. 203*:803-816 (1987)). This refinement was followed by manual rebuilding with FRODO using experimental and $2F_o$-F_c maps. The model can be optionally further refined using a least-squares refinement program, such as TNT (Tronrud *et al.*, *Acta Crystallogr. A 43*:489-501 (1987)).

One or more of the above modeling steps is performed to provide a molecular 3-D model of BPI. It is preferred that the BPI model has no residues in disallowed regions of the Ramachandran plot, and gives a positive 3D-1D profile (Luthy *et al.*, *Nature 356*:83-85 (1992)), suggesting that all the residues are in acceptable environments (Kraulis (1991), *infra*).

Multiple isomorphous replacement phase determination was used for solving the three-dimensional structure of BPI. This structure is then used for rational drug design of BPI ligands or mimetics of at least one BPI bactericidal activity, or other biological activity important in inactivating bacterial toxicity, replication and/or infection.

Computer Related Embodiments

An amino acid sequence of a BPI protein (or related protein such as LBP, CETP or PLTP) and/or x-ray diffraction data, useful for computer molecular modeling of BPI protein (or related protein such as LBP, CETP or PLTP) or a portion thereof, can be "provided" in a variety of mediums to facilitate use thereof. As used herein, provided refers to a manufacture, which contains, for example, a BPI amino acid sequence and/or atomic coordinate/x-ray diffraction data of the present invention, *e.g.*, an amino acid sequence provided in Figure 5, a representative fragment thereof, or an amino acid sequence having at least 80-100% overall identity to an amino acid fragment of an amino acid sequence of Figure 5 or a variant thereof. Such a method provides the amino acid sequence and/or x-ray diffraction data in a form which allows a skilled artisan to analyze and molecular model the three-dimensional structure of a BPI-related protein, including a subdomain thereof.

In one application of this embodiment, BPI (or related protein such as LBP, CETP or PLTP), or at least one subdomain thereof, amino acid sequence and/or x-ray diffraction data of the present invention is recorded on computer readable medium.

As used herein, "computer readable medium" refers to any medium which can be read and accessed directly by a computer. Such media include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as optical discs or CD-ROM; electrical storage media such as RAM and ROM; and hybrids of these categories such as magnetic/optical storage media. A skilled artisan can readily appreciate how any of the presently known computer readable mediums can be used to create a manufacture comprising computer readable medium having recorded thereon an amino acid sequence and/or x-ray diffraction data of the present invention.

As used herein, "recorded" refers to a process for storing information on computer readable medium. A skilled artisan can readily adopt any of the presently know methods for recording information on computer readable medium to generate manufactures comprising an amino acid sequence and/or atomic coordinate/x-ray diffraction data information of the present invention.

A variety of data storage structures are available to a skilled artisan for creating a computer readable medium having recorded thereon an amino acid sequence and/or atomic coordinate/x-ray diffraction data of the present invention. The choice of the data storage structure will generally be based on the means chosen to access the stored information. In addition, a variety of data processor programs and formats can be used to store the sequence and x-ray data information of the present invention on computer readable medium. The sequence information can be represented in a word processing text file, formatted in commercially-available software such as WordPerfect and MICROSOFT Word, or represented in the form of an ASCII file, stored in a database application, such as DB2, Sybase, Oracle, or the like. A skilled artisan can readily adapt any number of dataprocessor structuring formats (e.g. text file or database) in order to obtain computer readable medium having recorded thereon the information of the present invention.

By providing computer readable medium having stored thereon a BPI or related sequence protein and/or atomic coordinates based on x-ray diffraction data, a skilled artisan can routinely access the sequence and atomic coordinate or x-ray diffraction data to model a BPI or related protein, a subdomain thereof, mimetic, or a ligand thereof. Computer algorithms are publicly and commercially available which

allow a skilled artisan to access this data provided in a computer readable medium and analyze it for molecular modeling and/or RDD. *See, e.g.,* Biotechnology Software Directory, MaryAnn Liebert Publ., New York (1995).

The present invention further provides systems, particularly computer-based systems, which contain the sequence and/or diffraction data described herein. Such systems are designed to do structure determination and RDD for a BPI or related protein or at least one subdomain thereof. Non-limiting examples are microcomputer workstations available from Silicon Graphics Incorporated and Sun Microsystems running UNIX based, Windows NT or IBM OS/2 operating systems.

As used herein, "a computer-based system" refers to the hardware means, software means, and data storage means used to analyze the sequence and/or x-ray diffraction data of the present invention. The minimum hardware means of the computer-based systems of the present invention comprises a central processing unit (CPU), input means, output means, and data storage means. A skilled artisan can readily appreciate which of the currently available computer-based systems are suitable for use in the present invention. A visualization device, such as a monitor, is optionally provided to visualize structure data.

As stated above, the computer-based systems of the present invention comprise a data storage means having stored therein a BPI or related protein or fragment sequence and/or atomic coordinate/x-ray diffraction data of the present invention and the necessary hardware means and software means for supporting and implementing an analysis means. As used herein, "data storage means" refers to memory which can store sequence or atomic coordinate/x-ray diffraction data of the present invention, or a memory access means which can access manufactures having recorded thereon the sequence or x-ray data of the present invention.

As used herein, "search means" or "analysis means" refers to one or more programs which are implemented on the computer-based system to compare a target sequence or target structural motif with the sequence or x-ray data stored within the data storage means. Search means are used to identify fragments or regions of a BPI or related protein which match a particular target sequence or target motif. A variety of known algorithms are disclosed publicly and a variety of commercially available software for conducting search means are and can be used in the computer-based

systems of the present invention. A skilled artisan can readily recognize that any one of the available algorithms or implementing software packages for conducting computer analyses can be adapted for use in the present computer-based systems.

As used herein, "a target structural motif," or "target motif," refers to any rationally selected sequence or combination of sequences in which the sequence(s) are chosen based on a three-dimensional configuration or electron density map which is formed upon the folding of the target motif. There are a variety of target motifs known in the art. Protein target motifs include, but are not limited to, enzymic active sites, structural subdomains, epitopes, functional domains and signal sequences. A variety of structural formats for the input and output means can be used to input and output the information in the computer-based systems of the present invention.

A variety of comparing means can be used to compare a target sequence or target motif with the data storage means to identify structural motifs or electron density maps derived in part from the atomic coordinate/x-ray diffraction data. A skilled artisan can readily recognize that any one of the publicly available computer modeling programs can be used as the search means for the computer-based systems of the present invention.

One application of this embodiment is provided in Figure 6. Figure 6 provides a block diagram of a computer system 102 that can be used to implement the present invention. The computer system 102 includes a processor 106 connected to a bus 104. Also connected to the bus 104 are a main memory 108 (preferably implemented as random access memory, RAM) and a variety of secondary storage memory 110, such as a hard drive 112, a removable medium storage device 114, a command device 118, and a visualization device, 120. Also included is a removable storage medium 116. The removable medium storage device 114 may represent, for example, a floppy disk drive, a CD-ROM drive, a magnetic tape drive, etc. A removable storage medium 116 (such as a floppy disk, a compact disk, a magnetic tape, etc.) containing control logic and/or data recorded therein may be inserted into the removable storage device 114. The computer system 102 includes appropriate software for reading the control logic and/or the data from the removable storage medium 116 once inserted in the removable medium storage device 114.

Amino acid, encoding nucleotide or other sequence and/or atomic coordinate/x-ray diffraction data of the present invention may be stored in a well known manner in the main memory 108, or any of the secondary storage devices 110, and/or a removable storage medium 116. Software for accessing and processing the amino acid sequence and/or atomic coordinate/x-ray diffraction data (such as search tools, comparing tools, etc.) reside in main memory 108 during execution. User commands are implemented through a command device 118, such as a keyboard. The visualization device 120 is optionally used to visualize the structure data.

Structure Determination

One or more computational steps, computer programs and/or computer algorithms are used to provide a molecular 3-D model of BPI or related protein, using amino acid sequence data from Figure 5 (or fragments or variants thereof) and/or atomic coordinate/x-ray diffraction data. In x-ray crystallography, x-ray diffraction data and phases are combined to produce electron density maps in which the three-dimensional structure of a BPI protein is then built or modeled. MIR Phase determination was used for solving the three-dimensional structure of BPI. This structure can then be used for RDD of mimetics or ligands of a BPI or related protein and its associated biological activity, which is relevant to a protein modulated disease.

Density Modification and Map Interpretation

Electron density maps were calculated by X-PLOR or alternatively using such programs as those from the CCP4 computing package (SERC (UK) Collaborative Computing Project 4, Daresbury Laboratory, UK, 1979). If non-crystallographic symmetry axes are present, cycles of symmetry averaging can further be used, such as with the program RAVE (Kleywegt & Jones, Bailey *et al., eds., First Map to Final Model*, SERC Daresbury Laboratory, UK, pp 59-66 (1994)) and gradual model expansion. For map visualization and model building the program FRODO was used or alternatively, a program such as "O" (Jones (1991), *infra*) can be used.

Refinement and Model Validation

Rigid body and positional refinement can be carried out using a program such as X-PLOR (Brünger (1992), *infra*), *e.g.*, with the stereochemical parameters of Engh and Huber (*Acta Cryst. A47*:392-400 (1991)). If the model at this stage in the

averaged maps is still missing residues (*e.g.*, at least 5-10 per subunit), some or all of the missing residues can be incorporated in the model during additional cycles of positional refinement and model building. The refinement procedure can start using data from lower resolution (*e.g.*, 25-10Å to 10-3.0 Å and then be gradually extended to include higher resolution data from 12-6Å to 3.0-1.5 Å). B-values (also termed temperature factors) for individual atoms were refined once data between 2.9 and 1.5 Å has been added. Subsequently waters were gradually added by manual inspection of electron density maps. Alternatively, a program such as ARP (Lamzin and Wilson, *Acta Cryst. D49*:129-147 (1993)) can be used to add crystallographic waters and as a tool to check for bad areas in the model. The programs PROCHECK (Lackowski *et al., J. Appl. Cryst. 26*:283-291 (1993)), WHATIF (Vriend, *J. Mol. Graph. 8*:52-56 (1990)), PROFILE 3D (Lüthy *et al., Nature 356*:83-85 (1992)), and ERRAT (Colovos & Yeates *Protein Science, 2*:1511-19 (1993)) as well as the geometrical analysis generated by X-PLOR were used to check the structure for errors. Anisotropic scaling between F_{obs} and F_{calc} was applied after careful assessment of the quality and completeness of the data.

The program DSSP was used to assign the secondary structure elements (Kabsch and Sander, *Biopolymers, 22*:2577-2637 (1983)). A program such as SUPPOS (from the BIOMOL crystallographic computing package) can be used for some or all of the least-squares superpositions of various models and parts of models. The program ALIGN (Cohen *J. Mol. Biol., 190*: 593-604 (1986)) was used to superimpose N- and C-terminal domains of BPI. Solvent accessible surfaces and electrostatic potentials can be calculated using such programs as GRASP (Nicholls *et al.* (1991), *infra*).

The structure of BPI from different organisms and the related proteins LBP, CETP and PLTP can thus be solved with the molecular replacement procedure such as by using X-PLOR (Brünger (1992), *infra*). A partial search model for a portion or all of these proteins can be constructed using the structures of BPI. The rotation and translation function can be used to yield orientations and positions for these models. Symmetry averaging can also be done using the RAVE program and model expansion can also be used to add missing residues resulting in a model with 95-99.9% of the total number of residues. The model can be refined in a program such

as X-PLOR (Brünger (1992), *supra*), to a suitable crystallographic R_{factor}. The model data is then saved on computer readable medium for use in further analysis, such as rational drug design.

Rational Design of Mimetics or Ligands

The determination of the crystal structure of a BPI protein, as described herein, provides a basis for the design of new and specific agents, including proteins or organic compounds.

Several approaches can be taken for the use of the crystal structure of a BPI in the rational design of protein or organic analogs having a relevant activity similar to that of a BPI or related protein. A computer-assisted, manual examination of a BPI potential binding site structure is optionally done. The use of software such as GRID — Goodford, *J. Med. Chem. 28*:849-857 (1985) a program that determines probable interaction sites between probes with various functional group characteristics and the protein surface — is used to analyze the surface sites to determine structures of similar inhibiting proteins or compounds. The GRID calculations, with suitable inhibiting groups on molecules (*e.g.*, protonated primary amines) as the probe, are used to identify potential hotspots around accessible positions at suitable energy contour levels.

A diagnostic or therapeutic BPI or related protein modulating ligand of the present invention can be, but is not limited to, at least one selected from a lipid, a nucleic acid, a compound, a protein, an element, an antibody, a saccharide, an isotope, a carbohydrate, an imaging agent, a lipoprotein, a glycoprotein, an enzyme, a detectable probe, and antibody or fragment thereof, or any combination thereof, which can be detectably labeled as for labeling antibodies. Such labels include, but are not limited to, enzymatic labels, radioisotope or radioactive compounds or elements, fluorescent compounds or metals, chemiluminescent compounds and bioluminescent compounds. Alternatively, any other known diagnostic or therapeutic agent can be used in a method of the invention. Suitable compounds are then tested for activities of a BPI protein or BPI mimetic.

The program DOCK (Kuntz et al. *J. Mol. Biol., 161*:269-288 (1982)) may be used to analyze an active site or ligand binding site and suggest ligands with complementary steric properties. Several methodologies for searching three-

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dimensional databases to test pharmacophore hypotheses and select compounds for screening are available. These include the program CAVEAT (Bacon et al. *J. Mol Biol., 225*: 849-858 (1992)) which uses databases of cyclic compounds which can act as "spacers" to connect any number of chemical fragments already positioned in the active site. This allows one skilled in the art to quickly generate hundreds of possible ways to connect the fragments already known or suspected to be necessary for tight binding. The program LUDI (Bohm et al. *J. Comput.-Aid. Mol. Des., 6*:61-78 (1992)) can determine a list of interactions sites into which to place both hydrogen bonding and hydrophobic fragments. LUDI then uses a library of approx. 600 linkers to connect up to four different interaction sites into fragments. Then smaller "bridging" groups such as -CH2- and -COO- are used to connect these fragments. For example, for the enzyme DHFR, the placements of key functional groups in the well-known inhibitor methotrexate were reproduced by LUDI. See also, Rotstein and Murcko, *J. Med. Chem., 36*:1700-1710 (1992)).

After preliminary experiments are done to determine the K_i of a ligand (*e.g.*, a lipid ligand) by BPI (or related) protein to a BPI (or related) protein, mimetic or fragment, the time-dependent nature of the inhibition by the BPI or related protein (*e.g.*, by the method of Henderson (*Biochem. J. 127*:321-333 (1972)) is determined.

For example, a lipid ligand and a BPI mimetic are pre-incubated in buffer. Reactions are initiated by the addition of detecting substrate. Aliquots are removed over a suitable time course and each quenched by addition into the aliquots of suitable quenching solution. The concentration of product are determined by known methods of detection. Plots of activity against time can be close to linear over the assay period, and are used to obtain values for the initial velocity in the presence (V_i) or absence (V_o) of, for example, a BPI mimetic. Error is present in both axes in a Henderson plot, making it inappropriate for standard regression analysis (Leatherbarrow, *Trends Biochem. Sci. 15*:455-458 (1990)). Therefore, K_i values are obtained from the data by fitting to a modified version of the Henderson equation for competitive inhibition:

$$Qr^2 + (E_t - Q - I_t)r - E_t = 0$$

where (using the notation of Henderson (*Biochem. J. 127*:321-333 (1972)):

$$Q = K_t \left(\frac{A_t + K_a}{K_a} \right)$$

and

$$r = \frac{V_o}{V_i}$$

This equation is solved for the positive root with the constraint that $Q = K_t((A_t + K_a) / K_a)$ using PROCNLIN from SAS (SAS Institute Inc., Cary, North Carolina, USA) which performs nonlinear regression using least-square techniques. The iterative method used is optionally the multivariate secant method, similar to the Gauss-Newton method, except that the derivatives in the Taylor series are estimated from the histogram of iterations rather than supplied analytically. A suitable convergence criterion is optionally used, *e.g.*, where there is a change in loss function of less than 10^{-8}.

Once modulating compounds are found, crystallographic studies of co-complexes, for example, BPI mimetics complexed to a ligand are performed. As used herein, a co-complex refers to a BPI protein, fragment, analog or variant thereof in covalent or non-covalent association with a chemical entity or compound. As a non-limiting example, BPI crystals are soaked for 2 days in 0.01-100 mM inhibitor compound and x-ray diffraction data are collected on an area detector and/or an image plate detector (*e.g.*, a Mar image plate detector) using a rotating anode x-ray source. Data are collected to as high a resolution as possible, *e.g.*, ≤3.0 Å, and merged with a suitable *R*-factor on intensities. An atomic model of the mimetic is built into the difference Fourier map ($F_{\text{inhibitor complex}} - F_{\text{native}}$). The model can be refined to convergence in a cycle of simulated annealing (Brünger (1987), *infra*) involving 10-100 cycles of energy refinement, 100-10,000 1-fs steps of room temperature dynamics and/or 10-100 more cycles of energy refinement. Harmonic restraints may be used

for the atom refinement, except for atoms within a 10-15 Å radius of the inhibitor. An *R*-factor is calculated for the model as well as an r.m.s. deviation from the ideal bond lengths and angles.

Direct measurements of activity provide further confirmation that the modeled mimetic compounds are high-affinity inhibitors for the lipid ligands. Other suitable assays for biological activity known for BPI or related proteins may be used.

Preferably, little or no change in the structure of the BPI or mimetic occurs in the electron density map described above. K_i values are determined by a previously described method (Henderson (1972), *infra*) to evaluate mimetic proteins or organic compounds.

Atomic coordinates of BPI proteins are useful in the generation of molecular models of related proteins and of BPI mimetics. The atomic coordinates generated from the solved three-dimensional structure of BPI disclosed herein may be utilized in combination with additional structural and/or physicochemical information, such as amino acid sequence data, x-ray diffraction data, combinations of x-ray diffraction data from multiple isomorphous replacement molecular replacement techniques, or other phase determination techniques. These combinations may be used to generate other three-dimensional coordinate data useful to generate secondary, tertiary and/or quaternary structures and/or domains of BPI or related proteins, including BPI-related lipid binding proteins, or their fragments, analogs, or variants. These alternate coordinate sets are useful to provide overall three-dimensional structure, as well as binding and or active sites of a BPI or related protein, including BPI-related lipid binding proteins, or their fragments, analogs, or variants. These alternate coordinate data sets are also useful in molecular modeling computer-based systems and methods for rational drug design of mimetics and ligands of BPI and other related proteins, including other BPI-related lipid binding proteins. Utilizing CLUSTAL (a multiple sequence alignment program in PC-Gene) and the Homology module (a structure-based homology modeling program in InsightII on a Silicon Graphics Incorporated workstation, molecular models (and the corresponding three-dimensional coordinates files) of lipopolysaccharide binding protein (LBP), cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP) are generated. With these files, existing mutants are mapped and new ones designed.

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The results described herein demonstrate that tight-binding mimetics of a BPI or related protein, based on the crystal structure of BPI, are provided by the present invention. Demonstration of clinically relevant levels of a biological activity of the mimetic is also useful.

In evaluating mimetics for biological activity in animal models (*e.g.*, mouse, rat, rabbit, baboon) various oral and parenteral routes of administration are evaluated. Using this approach, it is expected that a biological activity occurs in suitable animal models, *e.g.*, using the mimetics discovered by structure determination and x-ray crystallography.

Having now generally described the invention, the same will be more readily understood through reference to the following examples which are provided by way of illustration, and are not intended to be limiting of the present invention.

Example 1: Preparation and Purification for Crystallization Construction of Plasmids Containing BPI (S351A)

BPI contains a single N-linked glycosylation site at the asparagine at position 349 which was eliminated by genetic engineering of the DNA sequence of BPI as follows. For glycosylation to occur at this position, the asparagine must occur within the sequence Asn-X-Ser/Thr where X can be any amino acid, except proline. N-linked glycosylation can be eliminated by either changing the Asn to another amino acid such as glutamine or by changing the serine or threonine to an alternate amino acid. The latter strategy was used to construct vectors containing BPI with an alanine at position 351 instead of serine.

Construction of Plasmids for BPI Expression

The plasmid pIC108 containing a cDNA encoding BPI cloned in a T3T7 plasmid (Clontech, Palo Alto, CA) served as the starting point for the construction of a vector for expression of nonglycosylated rBPI in mammalian cells.

To allow insertion of BPI into an optimized mammalian expression vector, a unique *Xho*I site was first added to the 3´ end of the BPI gene in pIC108. Two oligonucleotides were synthesized for this purpose: BPI-53 (5´ ACT GGT TCC ATG GAG GTC AGC GCC 3´) encoding amino acids 361 - 370 of BPI and BPI-54 (5´ GAC AGA TCT CTC GAG TCA TTT ATA GAC AA 3´) encoding the last four

amino acids of coding sequence, the stop codon (TGA), and incorporating an *Xho*I site immediately downstream of the stop codon. These oligonucleotides were used to PCR amplify a 280 bp fragment of the C-terminus of BPI and incorporate the *Xho*I site at the 3´ end of the gene. The amplified fragment was digested with *Nco*I and *Bgl*II and ligated to a ~4100 bp NcoI-BamHI fragment from pIC108 to generate the plasmid pSS101.

Construction of Plasmid with BPI (S351A)

The glycosylation site was next removed by replacing the region from a unique *Xcm*I site to a unique *Sph*I site within the BPI gene in pSS101 with an annealed oligonucleotide that contained the codon (TCC) for the serine at amino acid position 351 changed to the codon (GCC) for alanine as shown below.

```
Wild type
     XcmI                                                SphI
...CCC AAC TCC TCC CTG GCT TCC CTC TTC CTG ATT GGC ATG CAC
...GGG TTC AGG AGG GAC CGA AGG GAG AAG GAC TAA CCG TAC GTG
   Pro Asn Ser Ser Leu Ala Ser Leu Phe Leu Ile Gly Met His
               351
Nonglycosylated
     XcmI                                    -           SphI
...CCC AAC TCC GCC CTG GCT TCC CTC TTC CTG ATT GGC ATG CAC
...GGG TTC AGG CGG GAC CGA AGG GAG AAG GAC TAA CCG TAC GTG
   Pro Asn Ser Ala Leu Ala Ser Leu Phe Leu Ile Gly Met His
               351
```

This step generated the plasmid pSS102.

To construct the vector, pING4322, for the expression of full length nonglycosylated holo BPI in mammalian cells, pSS102 was digested with *Bst*BI and *Xho*I and a 596 bp fragment, which included the modified BPI sequence, was purified and ligated to the large *Bst*BI-*Xho*I fragment from pING4147 which contains the gpt gene encoding resistance to mycophenolic acid, the human Ig enhancer, the human cytomegalovirus promoter (CMV) and the mouse light chain 3' untranslated region and is identical to the vector, pING4144 as described in U.S. Patent No. 5,420,019 and WO94/18323 (PCT/US94/01235) hereby incorporated by reference, except that it contains the codon for the native cysteine instead of an alanine at amino acid position 132 of the BPI gene.

Stable Transfection of Mammalian Cells for Expression of Nonglycosylated BPI

Mammalian cells are preferred hosts for production of rBPI protein analogs as described herein. Such cells permit proper secretion, folding, and post-translational modification of expressed proteins. Presently preferred mammalian host cells for production of BPI proteins include cells of fibroblast origin, such as CHO-K1 cells (ATCC CCL61), CHO-DG44 cells (a dihydrofolate reductase [DHFR] minus mutant of CHO Toronto obtained from Dr. Lawrence Chasin, Columbia University), CHO-DXB-11 (a DHFR$^-$ mutant of CHO-K1 obtained from Dr. Lawrence Chasin), Vero Cells (ATCC CRL81) and Baby Hamster Kidney (BHK) cells (ATCC CRL6281) and cells of lymphoid origin, such as the hybridoma Sp2/O-Ag14 (ATCC CRL1581) or the myeloma, NSO (ECACC No. 85110503).

Transfection of mammalian cells can be accomplished by a variety of methods. Two of the most common approaches involve calcium phosphate precipitation of the expression vector DNA which is subsequently taken by the cells and electroporation, which causes the cells to take up the DNA through membrane pores created by the generation of a strong electric field. Selection for transfected cells is facilitated by the incorporation in the expression vector of a gene whose product allows the transfected cells to survive and grow under selective conditions. A number of such genes have been identified including, among others, the bacterial Tn5 *neo* gene, which encodes resistance to the antibiotic G418 and the *Escherichia coli* guanine phosphoribosyl transferase (gpt) gene, which encodes resistance to mycophenolic acid (MPA) in the presence of xanthine (Mulligan and Berg, *Proc. Natl. Acad. Sci.* 78:2072-2076 (1981)), the dihydrofolate reductase (DHFR) gene, which allows for growth of DHFR$^-$ cells in the absence of nucleosides and gene amplification in the presence of increasing concentrations of methotrexate, the glutamine synthetase gene, which allows for growth of glutamine auxotrophs without glutamine and gene amplification in the presence of methionine sulfoximine and the *Salmonella typhimurium hisD* gene and the *E. coli trpB* gene (Hartman and Mulligan, *Proc. Natl. Acad. Sci.* 85: 8047-8051 (1988)), which allow growth in the presence of histidinol or without tryptophan (in the presence of indole), respectively. The availability of these selective markers provide significant flexibility for the generation of mammalian cell lines that express recombinant products, since they can be used either alone or in various combinations to provide cell lines with the highest possible productivity.

Transfection of CHO-K1 Cells with pING4322

The CHO-K1 cell line was maintained in Ham's F12 medium plus 10% fetal bovine serum (FBS). Media were supplemented with glutamine/penicillin/streptomycin (Irvine Scientific, Irvine, California).

CHO-K1 cells were transfected by electroporation with 40 μg of pING4322 DNA that was first digested with *Pvu*I, phenol-chloroform extracted and ethanol precipitated. Following the electroporation, the cells were allowed to recover for 24 hours in non-selective Ham's F12 medium. The cells were then trypsinized, resuspended at a concentration of $\sim 5 \times 10^4$ cells/ml in Ham's F12 medium supplemented with MPA (25 μg/mL) and xanthine (250 μg/mL) and plated at $\sim 10^4$ cells/well in 96 well plates. Untransfected CHO-K1 cells are unable to grow in this medium due to the inhibition of pyrimidine synthesis by the MPA. At ~2 weeks, colonies consisting of transfected cells were observed in the 96 well plates. Supernatants from wells containing single colonies were analyzed for the presence of BPI-reactive protein by anti-BPI ELISA using BPI_{23} as a standard. In this assay, Immulon-II 96 well plates (Dynatech) were pre-coated with affinity purified rabbit anti-BPI_{23} antiserum, followed by supernatant samples and detection was with affinity purified, biotinylated rabbit anti-BPI_{23} antiserum followed by peroxidase-labeled avidin. A total of 100 colonies were screened in this manner. The top isolates were transferred to 24 well plates and productivity was assessed as follows. Cells were grown to confluence in a 24 well plate in Ham's F12 medium supplemented with 10% FBS. Once the cells reached confluence, the Ham's F12 medium was removed and 2 ml of HB-CHO serum free medium (Irvine Scientific) plus 40 μL of S-Sepharose beads (Pharmacia) were added. The cells were incubated for 7 days after which the S-Sepharose beads were removed and washed with 0.1 M NaCl in 10 mM Tris buffer (pH 7.5). BPI was eluted from the beads by addition of 1.0 M NaCl in Tris buffer. The top producers, designated Clones 37 and 91, secreted ~17 and 14 μg/ml, respectively in this assay and were frozen as Research Cell Bank numbers C2020 and C2021, respectively. Purified protein was prepared for crystallization studies as follows.

Production and Purification of Nonglycosylated rBPI.

The host cells used to prepare protein for crystallization studies were CHO-K1 cells transformed with the DNA vector pING4322 which includes DNA encoding the 456 amino acids of human BPI preceded by its endogenous 31 residue secretory signal as described above. During post-translational secretory processing, the signal sequence residues were removed by the host cell. The desired expression product, nonglycosylated rBPI, was a biologically active variant of the human BPI molecule in which the amino acid serine at position 351 in the human BPI protein has been replaced with an alanine.

Forty roller bottles were prepared which contained the transfected CHO-K1 host cells at 1.3 x 10^7 cells per bottle in DME/F12 media supplemented with 5% fetal bovine serum (FBS). The cells were grown for three days, at which time 500 ml of fresh media, DME/F12 with 2.5% FBS was added along with a 10 ml slurry (approximately 8 gr.) of sterilized S-Sepharose (Pharmacia, fast flow #17-0511-01, Uppsula, Sweden) and 1 ml of a 1 M solution of sodium butyrate. After two days, the old media plus the S-Sepharose was removed and fresh media, S-Sepharose and sodium butyrate were added to each roller bottle. This process of harvesting the expressed protein product with S-Sepharose was repeated for a total of three harvests, and the S-Sepharose removed during each harvest was pooled. The use of S-Sepharose beads to capture recombinant BPI protein products has been described in U.S. Patent No. 5,439,807 and WO93/23540 (PCT/US93/04752).

The expressed nonglycosylated rBPI protein was purified from the pooled S-Sepharose by first removing it from the S-Sepharose resin followed by further purification and concentration on a series of Q-Sepharose (Pharmacia, fast flow #17-0510-01) and CM-Spherodex (Sepracor, #273431, Villeneuve la Garenne, France) columns. Following purification, the protein was buffer exchanged utilizing a Sephacryl S-100 (Pharmacia, high resolution #17-0612-01) column.

Specifically, the pooled S-Sepharose resin from each harvest was allowed to settle for approximately 15 minutes. The media was removed by decanting and the settled resin was washed three times with approximately 400 ml of 20 mM MES, pH 6.8, 150 mM NaCl. For each wash, the buffer was added, the mixture was stirred gently and the resin was allowed to resettle for approximately 15 minutes. Each buffer wash was removed by decanting. The beads were then washed with 400 mL

of 20 mM sodium acetate/acetic acid, 150 mM NaCl, pH 4.0 (acetate buffer), and then poured into a 2.5 x 50 cm liquid chromatography column (BIORAD, Econocolumn, Richmond, California). The column was washed extensively with approximately 2 liters of 400 mM NaCl-acetate buffer, pH 4.0 until the A280 absorbance reading of the column eluate was equal to that of the buffer alone. The column was additionally washed with approximately 600 ml of 600 mM NaCl-acetate buffer until the A280 absorbance of the eluate was again equal to that of buffer alone. The protein was then eluted from the S-Sepharose in approximately 500 ml of 1.0 M NaCl-acetate buffer.

The S-Sepharose eluates from each harvest were pooled and diluted to a NaCl concentration of 300 mM. The diluted material was then loaded on to a two column, serial arrangement of a 100 ml Q-Sepharose column connected to a 12 ml CM-Spherodex column. Both columns were constructed using new, sterile resin and were pre-equilibrated with 20 mM MES, pH 5.5, 200 mM NaCl. The Q-Sepharose column served to remove any nucleic acid in the sample material, and the protein did not bind to this resin. After the approximate 3 liters of protein containing material had been loaded, the Q-Sepharose column was disconnected and the CM-Spherodex column was washed with buffer until the A280 absorbance of the eluate was the same as buffer alone. The protein was eluted from the column in 20 mM MES, 400 mM NaCl, pH 5.5 in a volume of approximately 180 ml. This eluted fraction was then reloaded on to a smaller (2 ml) CM-Spherodex column for protein concentration, and the bound protein removed in a single step of 20 mM MES, 1.2 M NaCl, pH 5.5 in a volume of approximately 12 mL. The protein was then loaded directly on to a 150 ml pyrogen-free Sephacryl S-100 column pre-equilibrated with 20 mM sodium citrate, 150 mM NaCl, pH 5.0 buffer. Column fractions were analyzed by Coommassie-stained (0.5% Coommassie Brilliant Blue-R, 25% isopropanol, 10% methanol, 10% acetic acid) SDS-PAGE and Western analysis. Western analysis was performed using a 1:1000 dilution of a rabbit anti-human BPI antisera. Fractions which contained the nonglycosylated rBPI protein were pooled and resulted in a final lot which was greater than 95% pure as analyzed by Coommassie-stained SDS-PAGE.

The protein samples thus prepared and purified were filtered and/or concentrated for crystallization studies of the purified nonglycosylated rBPI protein.

Protein samples were optionally filtered using a 0.2 μm syringe filter (Millipore Corp., Bedford, MA) or a 0.2 μm Nalgene filter (Nalge Corp., Rochester, NY) to remove precipitate. Protein samples were concentrated in a Centricon 10 (Amicon Corp., Beverly, MA) or a Centriprep 10 (Amicon Corp., Beverly, MA). For the Centricon 10 concentrators, a JA 20 rotor (Beckman, Fullerton, CA) in a J2-21 Beckman centrifuge was used at 6000 rpm for 60 minutes. For the Centriprep 10 concentrators, a swinging bucket rotor in a J-6B Beckman centrifuge was used at 3000 rpm for 60 minutes. Final volumes for various protein samples prepared for crystallization studies described herein ranged from about 0.1 to 1 mL, and the protein concentrations were generally between about 10 and 20 mg/mL. Protein solutions may be diluted or concentrated for crystallization studies, for example, from about 5 to about 50 mg/ml.

Example 2: Structure Determination of a Crystallized BPI Protein

Presented herein is the crystal structure of BPI and two bound phospholipids at 2.4 Å resolution. Our model provides the first structural information on the LPS-binding and lipid transport protein family and suggests a common mode of lipid binding for its members.

Purified, full-length, non-glycosylated, recombinant human BPI expressed in CHO cells was crystallized by hanging-drop vapor diffusion at room temperature. The protein concentration was 8.5 mg/ml and the crystallization buffer contained 12% (w/v) PEG 8000, 200 mM magnesium acetate, and 100 mM sodium cacodylate, pH 6.8. Two crystal forms with slightly different cell dimensions grew under the same conditions in space group C_2, with one molecule per asymmetric unit. Form 1 crystals were reproducible and had cell dimensions of $a=185.0$, $b=37.2$, $c=84.3$ Å, and $\beta=101.3^{\circ}$. Form 2 crystals appeared rarely and had cell dimensions of $a=185.6$, $b=33.0$, $c=85.2$ Å, and $\beta=101.6^{\circ}$

For Table 1, x-ray diffraction data were collected at room temperature with the R-AXIS IIC imaging plate area detector mounted on a Rigaku RU200 rotating anode x-ray generator. Data were processed with DENZO and SCALEPACK [Z. Otwinski, in *Proceedings of CCP4 Study Weekend: Data Collection and*

Processing, L. Sawyer, N. Isaacs, S. Baileys, Eds. (SERC Daresbury Laboratory, Warrington, UK, 1993), pp. 56]. For form 1 crystals, a native data set to 2.8 Å was collected from a single crystal, which was 92.4% complete overall (84.9% complete with an average $I/\sigma(I)=2.3$ in the outermost resolution shell). A native data set to 2.4 Å for form 2 was collected from two crystals and was 92.7% complete overall (94.6% complete with an average $I/\sigma(I)=2.6$ in the outermost shell). Because they could be reliably reproduced, form 1 crystals were used for all heavy atom soaks. The structure was solved by multiple isomorphous replacement (MIR) with anomalous scattering. Heavy atom sites were identified by difference-Patterson and difference-Fourier maps. Phase refinement was performed with [Collaborative Computational Project No. 4, *Acta Crystallogr., D50*:760 (1994)] producing a mean figure of merit (FOM) of 0.57. The MIR map (Fig. 3) was improved by density modification including solvent flattening, histogram matching, and phase extension using DM [Collaborative Computational Project No. 4, *supra*]. After a partial model was obtained with FRODO [T. A. Jones, *J. Appl. Crystallogr., 11*:268 (1978)], phase combination was performed with SIGMAA [Collaborative Computational Project No. 4, *supra*] (final FOM=0.89). CMNP is chloro-Hg-nitrophenol; DMM is dimethyl mercury; PCMBS is parachloromercury-benzene sulfonate; TELA is triethyl lead acetate.

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TABLE 1: X-RAY DIFFRACTION DATA

Item	Resolution (Å)	Data Completeness	R*sym** (%)	Sites (N)	R*Cullis*†	Phasing Power	Mid‡
Native 1	2.8	92.4	8.6				
Native 2	2.4	92.7	7.2				
CMNP§	3.2	84.8	6.1	1	66.0	2.04	0.15
DMM‖	3.5	72.8	9.8	11	65.0	1.49	0.26
PCMBS¶	3.1	66.4	9.4	3	77.0	1.27	0.38
$HgCl_2$	3.0	86.5	6.9	1	49.0	2.13	0.18
K_2PtCl_4	3.2	93.3	8.2	3	90.0	0.68	0.13
K_2PtBr_6	3.1	94.8	5.8	3	73.0	0.88	0.14
TELA#	3.3	94.0	11.3	2	86.0	0.80	0.15
TELA-$HgCl_2$	3.3	91.4	9.6	3	63.0	1.90	0.18
Xenon	3.4	98.2	18.9	5	87.0	0.69	0.18
$K_3UO_2F_5$	3.0	75.0	8.6	2	65.0	1.40	0.16

*$R_{sym} = 100\ (\Sigma_h \mid |_h - \langle | \rangle |)/(\Sigma h\ |h)$ where $\langle | \rangle$ is the mean intensity of all symmetry-related reflections $|h$.

†$R_{Cullis} = (\Sigma|F_{PH} +/- F_P| - F_{H(calc)})/(\Sigma|F_{PH} +/- F_P|)$ for centric reflections, Phasing power $= [\Sigma| F_{H(calc)}{}^2|/ (\Sigma\ |F_{PH(obs)} - F_{PH(calc)}\ |^2]^{1/2}$.

‡MID (mean isomorphous difference) $= \Sigma\ |\ F_{PH} - F_P|/\Sigma\ F_P$, where F_{PH} is the derivative structure factor and F_P is the native structure factor and the sum is over all reflections common to both data sets.

§CMNP, chloro-Hg-nitrophenol; ‖DMM, dimethyl mercury; ¶PCMBS, parachloromercurybenzene sulfonate; #TELA, triethyl lead acetate

Table 2 relates to model refinement and statistics. The model was refined at 2.8 Å through iterative cycles of simulated-annealing with X-PLOR [A. T. Brünger and A. Krukowski, *Acta Crystallogr., A46*:585 (1990)] and manual rebuilding. 10% of the data were set aside before refinement began for R_{free} [A. T. Brünger *Nature, 355*:472 (1992)] calculations. When the model had been refined to an R-factor* of 20.4% (R_{free}=32.6%) with the 2.8 Å data, rigid-body minimization was performed against the 2.4 Å data set (R=29.8% to 3.5 Å after minimization). Additional cycles of simulated annealing, positional refinement, correlated individual temperature factor refinement, and manual rebuilding reduced the R-factor to 22.7% and R_{free}=31.3% (no intensity cutoff). An overall anisotropic temperature factor and bulk solvent correction were applied to the observed reflections when R_{free} showed improvement. The model was confirmed by calculating simulated-annealing omit-maps for every part of the structure. The final model contains all 456 residues of the protein, 48 well-ordered waters, and 2 molecules of phosphatidylcholine. Regions of the backbone with poor electron density include residues 148, 232-236, 258-260, and parts of the loop between residues 281-311. Sidechains with poorly defined density were truncated to alanine. The model was examined by the programs PROCHECK [R. A. Laskowski, M. W. McArthur, D. S. Moss, J. M. Thornton, *J. Appl. Crystallogr. 26*:283 (1993)], VERIFY [R. Lüthy, J. U. Bowie, D. Eisenberg, *Nature, 356*:83 (1992)], and ERRAT [C. Colovos and T. Yeates, *Protein Sci., 2*:1511 (1993)].

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TABLE 2: REFINEMENT STATISTICS FOR FORM 2 CRYSTALS

Data	
Resolution (Å)	2.4
Unique reflections (N)	18,898
Completeness (%)	92.7
Atoms in model	
Protein (non-hydrogen)	3532
Phosphatidylcholine	102
Water	48
Refinement parameters	
Resolution range (Å)	50.0-2.4
R-factor* (%)	22.7
R_{free}(%)	31.3
Avg. atomic B factors	
Protein	36.9
Lipid N, C	49.4, 51.0†
Waters	44.6
rms‡ deviation from ideality	
Bonds (Å)	0.006
Angles (deg)	1.4
Dihedrals (deg)	26.0
Impropers (deg)	1.2

*R = 100 (Σ | F_{obs} - F_c |)/(Σ F_{obs}) where F_{obs} and F_c are the observed and calculated structure factors, respectively.
†B factors for the lipids bound in the NH_2- and COOH-terminal domains.
‡rms=root mean square

BPI is a boomerang-shaped molecule with approximate dimensions of 135 by 35 by 35 Å (Fig. 1, A and B). It consists of two domains of similar size (NH_2- and COOH-terminal) that are connected by a proline-rich linker of 21 residues (positions 230 to 250). The two domains form three structural units; barrels are found at each end of the protein, and a central β sheet forms an interface between the barrels. The secondary structure and topology of the two domains are similar, giving the protein pseudo-twofold symmetry.

Each barrel (residues 10 to 193 and 260 to 421) contains three common structural elements: a short α helix, a five-stranded antiparallel β sheet, and a long helix (Fig. 2A), in that order. We call these elements helix A, sheet N and helix B in the NH_2-terminal domain, and helix A´, sheet C and helix B´ in the COOH-terminal domain. Sheets N and C have a series of β bulges that change the direction

of their strands and cause a pronounced curve in the sheets. In each domain, the long helix lies along the concave face of the sheet, with the helical axis at ~60° to the strands of the β sheet. A single disulfide bond between Cys^{135} and Cys^{175} anchors helix B to the final strand of sheet N. Situated between the NH_2- and COOH-terminal barrels is a twisted, seven-stranded antiparallel β sheet composed of four strands from the NH_2-terminal domain and three strands from the COOH-terminal domain. This central sheet forms an interface between the two domains and is thus reminiscent of several dimer interfaces stabilized by hydrogen bonds between strands of a β sheet [M. Leeson, B. Henderson, J. Gillig, J. Schwab and J. Smith, *Structure, 4*:253 (1996); D. Ohlendorf, W. F. Anderson, M. Lewis, C. O. Pabo, B. W. Matthews, *J. Mol. Biol., 169*:757 (1983); G. N. Reeke, J. W. Becker, G. M. Edelman, *J. Biol. Chem., 250*:1525 (1975)].

The structural similarity of the two domains of BPI is shown by the superposition [G. H. Cohen, *J. Mol. Biol., 190*:593 (1986)] in Fig. 2B; they are related by a rotation of 173° and have a root mean square deviation (rmsd) of 3.0 Å on the basis of superposition of 169 Cα pairs. The structure shared by these two domains does not resemble other protein folds; several structural alignment programs [N. N. Alexandrov and D. Fischer, *Proteins, 25*:354 (1996); D. Fischer, C. J. Tsai, R. Nussinov, *Protein Eng., 8*:981 (1995); L. Holm, C. Sander, *Nucl. Acids Res., 22*:3600 (1996)] failed to reveal a significant match to any known folds. Significant differences between the superimposed domains are found in two loop regions containing residues 45 and 96 in the NH_2-terminal domain and residues 280 and 348 in the COOH-terminal domain. These differences may be functionally important because the loops around residues 45 and 96 in the NH_2-terminal domain have been implicated in LPS binding and bactericidal activity (see below). This structural similarity of the two domains was unexpected, not only because of their lack of significant sequence identity (<20%), but also because of their functional differences. The NH_2-terminal domain of BPI is cationic and retains the bactericidal, LPS-binding, and LPS-neutralization activities of the intact protein [A. H. Horwitz, et al., *Protein Expr. and Purif., 8*:28 (1996); C. E. Ooi, J. Weiss, P. Elsbach, B. Frangione and B. Mannion, *J. Biol. Chem., 262*:14891-14894 (1987); C. E. Ooi, J. Weiss, M. E. Doerfler and P. Elsbach, *J. Exp. Med., 174*:649 (1991)]. The COOH-terminal

domain is essentially neutral and shows limited LPS-neutralization activity [S. L. Abrahamson et al., *J. Biol. Chem.*, *272*:2149 (1997)]. However, the structural similarity of the two domains may reflect a previously undetected functional similarity: each domain contains a binding pocket for a phospholipid.

After the amino acid sequence had been traced in the electron density maps, two regions of extended electron density remained that could not be accounted for by protein atoms. This density, found in the interior of both domains, was present in the multiple isomorphous replacement (MIR) maps (Fig. 3) at an intensity similar to that of the protein density, and it became the predominant feature in F_{obs}-F_{calc} maps after sequence fitting (both form 1 and form 2 crystals). Electrospray mass spectrometry of the sample used for crystallization revealed two molecules, with relative molecular masses of 522 and 787, in approximately equal amounts. Tandem mass spectrometric analysis was consistent with the two species being phosphoglycerides containing a phosphatidylcholine head group and either one or two 18-carbon acyl chains with one double bond. Phosphatidylcholine (Fig. 4A) is abundant in eukaryotic cells and is presumably bound by BPI in the cells from which the protein is isolated.

The two lipids are bound in extensive apolar pockets on the concave surface of the boomerang, situated between the NH_2-terminal and COOH-terminal barrels and the central β sheet. In the NH_2-terminal domain, the entrance to the pocket is formed by helices A and B. The back and sides are formed by sheet N and the central sheet. The two acyl chains insert ~15 Å into the interior of the protein and are surrounded by apolar side chains (Fig. 4B). The head group lies at the entrance of the pocket and is exposed to solvent. The pocket in the COOH-terminal domain, which has a slightly larger opening, is formed by the analogous secondary structures. Both basic and acidic side chains found near the entrances of the pockets are available for electrostatic interactions with the zwitterionic head group. When the lipids are removed from the model, the pocket in NH_2-terminal domain has a solvent accessible surface area [M. L. Connolly, *Science, 221*:709 (1983); M. L. Connolly, *J. Am. Chem. Soc., 107*:1118 (1985)] of 557 Å^2, and the pocket in the COOH-terminal domain has an area of 413 Å^2, for a total of 970 Å^2. The intensity of the electron

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density for the two acyl chains in both pockets is similar and does not indicate whether the single acyl chain species is found predominantly in either pocket.

The discovery of bound phospholipid in our structure suggests a possible site of interaction between BPI and LPS. As seen in Fig. 4A, phosphatidylcholine and LPS share some structural similarity, including negatively charged phosphate groups and, most notably, acyl chains. Since BPI's function is to bind a lipid, LPS, and since lipid is bound in pockets of BPI, it seems reasonable that the acyl chains of LPS bind in the apolar pockets. The following observations support his hypothesis: i) the acyl chains of lipid A are known to be essential for binding by BPI [H. Gazzano-Santoro et al., *Infection and Immunity, 63*:2201 (1995)]; ii) the binding pockets of BPI are reminiscent of cavities in other lipid-binding proteins [L. Banaszak et al., *Adv. Protein Chem., 45*:89 (1994)]; and iii) BPI has a significant sequence similarity to two lipid transfer proteins (see below).

Our proposed site of interaction between BPI and the acyl chains of LPS differs from that suggested by previous work focusing on the NH_2-terminal domain. Fragments containing the NH_2-terminal domain of BPI have been identified with equivalent or greater bactericidal and LPS-binding activities relative to the full-length protein [A. H. Horwitz, et al., *Protein Expression and Purification, 8*:28 (1996); C. E. Ooi, J. Weiss, M. E. Doerfler and P. Elsbach, *J. Exp. Med., 174*:649 (1991)]. The activity of one NH_2-terminal fragment was reduced when residues past positions 12 or between positions 169 and 199 were deleted [C. Capodici and J. Weiss, *J. Immunol., 156*:4789 (1996)]. The structure shows that these deletions affect elements of the barrel (at the beginning of helix A and from the middle to the end of helix B) and could significantly alter its structure. While the barrel seems to be the minimal structural unit with full activity, three smaller regions of this domain retain significant LPS-binding, LPS-neutralization, and bactericidal activity [R. G. Little, D. N. Kelner, E. Lim, D. J. Burke and P. J. Conlon, *J. Biol. Chem., 268*:1865 (1994)]: residues 17-45 (most of helix A and the first β strand of sheet N), residues 82-108 (a β hairpin [residues 82 to 106 of BPI show limited sequence similarity with residues 32 to 51 of the *limulus* anti-LPS factor (LALF), and have been predicted to form an amphipathic β hairpin similar to that seen in the LALF structure [A. Hoess, S. Watson, G. R. Silber and R. Liddington, *EMBO 12*:3351 (1993)]. Although this

region of BPI does form a β hairpin, the strict amphipathic character of the loop seen in LALF is not maintained, and a structural superposition shows that the sequence of BPI must be shifted by one residue relative to the proposed sequence alignment] between strands 3 and 4 of sheet N), and residues 142-169 (a segment preceding and including part of helix B). These three regions include 18 basic residues (and only 4 acidic residues) and form a positively charged tip on the NH_2-terminal domain (on the left of Fig. 1) which may make favorable electrostatic interactions with negatively charged groups of LPS. Further studies are necessary to determine the relative importance of the apolar pockets and positively charged NH_2-terminal tip to BPI's LPS-binding and bactericidal activities.

BPI is the first member of the mammalian LPS-binding and lipid transfer family to have its three-dimensional structure determined. BPI and LBP are related to two lipid transfer proteins, cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP) [A. Tall, *Annu. Rev. Biochem.*, *64*:235 (1995)]. Alignment of the amino acid sequences of human BPI, LBP, CETP, and PLTP with BPI's secondary structure (Fig. 5, A and B) shows that structurally important residues are conserved in the four proteins. The two cysteines that form the single disulfide bond and are critical to the function of BPI [A. H. Horwitz, et al., *Protein Expression and Purification*, *8*:28 (1996)] are completely conserved. Also, the pattern of hydrophobic/hydrophilic residues in the β strands indicates that the β bulges responsible for the extensive sheet twisting are preserved. The conserved sequences strongly suggest that members of the LPS-binding and lipid transfer family share BPI's two-domain structure and that the two domains are similar in topology.

It is likely that the lipid transfer proteins will also share the apolar binding pockets found in BPI. Striking parallels are found between our BPI-phosphatidylcholine structure and previous work showing that CETP copurifies with an equimolar amount of phosphatidylcholine [A. Tall, *Annu. Rev. Biochem.*, *64*:235 (1995)] and has two distinct binding sites [S. Wang, L. Deng, R. W. Milne and A. R. Tall, *J. Biol. Chem.*, *267*:17487 (1992)] -- one for neutral lipids and another for phospholipids. The known ligands of CETP and PLTP (cholesteryl esters, triglycerides, retinyl esters and phospholipids) all contain at least one acyl chain which could bind in apolar pockets similar to those in BPI, suggesting a common

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mode of ligand binding in this family. Sequestration of these hydrophobic chains in interior pockets may be critical to the function of the lipid transfer proteins: transfer of apolar ligands in an aqueous environment. Thus, the structure of BPI illuminates the action of the plasma lipid transfer proteins, as well as offering possibilities for how BPI and LBP interact with LPS.

Example 3: Molecular Modeling of BPI Ligands and Mimetics

We have used the information derived from the X-ray crystal structure of BPI presented herein, along with the teachings of the art, including, for example, WO94/20532 (PCT/US94/02465) to design various BPI-related proteins and peptides. These constructs may be divided into categories as illustrated below, including peptides and proteins, including fragments, analogs and variants of the protein, since they best describe the different ways in which different domains and portions may be assembled to achieve new molecules.

1. **Individual Peptide Domains**: The overlapping BPI peptide data indicated that the N-terminal domain of BPI contains at least three independent functional domains that have one or more of the biological activities of BPI, including, for example, antibacterial, antifungal, anti-heparin and anti-angiogenic activities. Domain I is a region of amino acid residues from about 17 to about 45; Domain II is a region of amino acid residues from about 65 to about 99; and Domain III is a region of amino acid residues from about 142 to about 169. Hundreds of peptide sequences derived from these domains have been synthesized, including addition, deletion and substitution variants of the domain-derived sequences. Through further refinements, smaller "core" regions within these domains have been identified that still retain high levels of activity; for example, within Domain II residues 90-99 and within Domain III residues 148-161.

These peptides have included linear molecules that may or may not assume a conformation that maximally express activity. From the X-ray structure data, segments of BPI are designed that should preserve the three-dimensional structure of these domains when constructed outside the context of the intact protein. For example, both Domains I and II contain hairpin loop structures that are positioned adjacent to one another in space on the proximal tip of the molecule. In contrast,

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although Domain III is a helix + turn and not a loop, extensions from both ends of the domain are positioned near enough to each other to consider linking them together. As a result, peptides can be designed that reflect these structures by replacing selected residues in synthetic or recombinant peptides with cysteines, so as to create disulfide-stablized domain mimetics. Since this approach is based upon the actual structure of BPI, it differs from those of other groups that are based upon putative alignments between BPI and the structure of proteins such as the *Limulus* amoebocyte lysate factor (LALF). As examples of these embodiments, listed below are a series of exemplary peptides that, with cysteines added to the N- and C-terminus could assume structures similar to those seen in the intact protein: from Domain I: residues 36-54; from Domain II: residues 84-109, 85-108, 86-107, 87-106, 88-105, 89-104, or 90-103; and from Domain III: residues 142-164.

2. **Peptide Domain Hybrids**: It has also been demonstrated that certain peptide domain hybrids, which include repeats of the same sequence from a single domain or inter-domain combination of sequences, have enhanced activities. For example, linking Domain II- and III-derived peptides (such as XMP.29: 85-99::148-161) has enhanced biological activity. Interestingly, these domains in the crystal structure are closely associated in space, and peptide XMP.29 may represent a Domain II::III hybrid that actually shares some structural similarity to the intact protein. Based upon the X-ray structure, a Domain II-III peptide that consists of approximately residues 90-103::146-162 is constructed. Such a peptide may even more closely mimic what is seen in the protein.

3. **BPI "Tip" Mimetics**: As discussed above, portions of all three peptide domains discovered and described in WO94/20532 come together on the proximal tip of the N-terminal fragment. As a result, a BPI "tip" mimetic is designed that essentially "slices" off the most extreme tip of the molecule but preserves the critical domain elements. Such a slice would lack the hydrophobic pockets found in the intact protein, but may exhibit activities beyond those of the individual segments. The following segments represent such a "slice" of the three peptide domains. However, to best preserve the geometry between the domains, it would be desirable to insert "linker" sequences between them so as to ensure proper positioning. By fixing these segments in space, programs such as InsightII (Molecular Simulations,

Inc.) can identify possible linker sequences by i) searching protein databases for similar structures or ii) *de novo* designing appropriate linkers. In this regard it may be desirable to utilize residues that are not readily susceptible to proteolysis (Ala, Ser, Gly, etc.), or to utilize amino acids like Pro that impose additional spatial constraints on peptide structure. An exemplary peptide consists of Domain I-II-III-derived elements: 37-54:90-104:144-162.

Similarly, by analogy with the above-described cyclic domain structures, the fact that residues 37 and 162 are positioned near each other in the protein suggests that a cyclic tip mimetic could be created by replacing these residues with cysteines, for example, Cys::38-54:90-104:144-161::Cys.

4. **Extended N-terminal Domains of BPI**: The three dimensional structure of BPI indicates that the molecule, which forms N- and C-terminal domains, can be divided into three structural units as described in Example 2. Two of these units represent the N- and C-terminal "barrels" that are formed by residues 10-193 and 260-421, respectively, whereas the third element is a central ß sheet structure that forms the interface between the two barrels. Of interest is the fact that the two bound phospholipids in BPI occupy spaces between the two barrel structures and the central ß sheet. As a result, the recombinant BPI protein product $rBPI_{21}$, which essentially contains residues 1-193 lacks some of the structural components necessary to form a complete hydrophobic pocket. A new molecule is constructed that encodes residues 1 to approximately 260 which would contain most of the residues necessary to form a complete hydrophobic pocket.

5. **Mutants for Immobilizing $rBPI_{21}$**: One application for BPI protein products is their use as affinity removal ligands for endotoxin in solution. For example, immobilizing a BPI protein on a column or membrane matrix would allow removal of endotoxin from endotoxin-contaminated solutions by simply passing those solutions over the immobilized BPI protein. Some of the cysteine-mutated peptides described above may be useful for this purpose, as well as $rBPI_{23}$. Alternatively, in order to selectively couple a stable, readily produced protein like $rBPI_{21}$ to a column or membrane, a cysteine could be added to the N- or C-terminus, thus allowing site-specific conjugation and selective orientation of the binding "tip" away from the solid support. Such a construct is alternatively constructed by adding a short linker

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segment (such as Gly-Gly-Gly-Ser) to the C-terminal residue of the BPI protein product, for example, residue 193 of rBPI(1-193), followed by a cysteine residue. Such a construct would have a high probability of folding correctly, given the domain nature of residues 1-193, and be readily conjugatable. Similarly, a series of new conjugates between rBPI(1-193)C and other thiol-containing proteins or molecules is created for the purposes of evaluating new molecules.

6. **New N-terminal Dimeric Molecules**: As an extension of the above analysis, a new series of N-terminal dimeric molecules can be constructed that take better advantage of the hydrophobic pockets. For example, by replacing the C-terminal barrel with another copy of the N-terminal barrel, an analog of BPI would be created that contains two functional barrels and possibly two functional hydrophobic pockets. One such dimer could be constructed by replacing residues 260-456 with residues 1-193. Alternatively, other more central locations may be identified within the ß sheet structure where symmetry would dictate additional and even better points for duplication.

7. **C-terminal Fusion Proteins**: The C-terminal domains of LBP and CETP appear to mediate interactions with CD14 and lipoproteins. Similarly, the C-terminal domain of BPI has LPS binding and neutralization activities. As a consequence, the C-terminal barrel of BPI (or other family members) could be fused to barrels or domains of other family members and/or to other proteins to alter/modify/enhance their action.

8. **Homology modeling of BPI family members**: The BPI coordinates have been useful in the generation of molecular models of other members of the BPI protein family. Utilizing CLUSTAL (a multiple sequence alignment program in PC-Gene) and the Homology module (a structure-based homology modeling program in InsightII on the SGI), molecular models (and the corresponding three-dimensional coordinates files) of lipopolysaccharide binding protein (LBP), cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP) have been generated. With these files, existing mutants are mapped and new ones designed. Published data [Wang et al., *Biochemistry 30*:3484-3490, (1991)] indicate that insertional alterations in three locations of CETP severely impaired cholesteryl ester transfer activity: residues 48-53, residue 165, and residues 373-379. Since residues

48-53 and residue 165 of CETP coincide structurally with Domains I and III of BPI respectively, the functional domain structure of BPI extends to the other protein family members. Similarly, by virtue of the symmetry between the N- and C-terminal domains, it is likely that the corresponding residues on the C-terminal tip of BPI are involved in recognizing receptors and/or interacting with lipoproteins.

9. **Lipid Pocket Mutants**: A detailed compilation of the residues in BPI which form the pockets is described in Table 3 as follows. Column 1 of Table 3 indicates the residue name and number. Column 2 shows checked residues which indicate the residues that show a change in solvent accessible surface area with lipid binding. Column 3 shows checked residues that indicate the residues that have some atom within 4 Å of a lipid atom. If the contact is to the head-group of the lipid, the residues are listed at the end, under ENTRY ONLY. Column 4 indicates conservation in 3 BPI and 4 LBP sequences, *e.g.*, for Ile 68, in 3 of the 7 sequences, the residue is similarly Ile; for the other 4 sequences, the residue is Leu (see also column 5). Column 5 indicates alternative residues which occur in BPI or LBP at that position for the 7 BPI and LBP sequences analyzed. Column 6 indicates residues for mutations to block the pockets, using residues selected to be well-conserved (especially in the N-terminal domain) and relatively small. The suggested mutations are all to large sidechains in order to decrease the size of the pocket by as much as possible.

TABLE 3

N-TERMINAL POCKET - residues contributing to interior					
Residue[1]	ΔSA[2]	Within 4Å[3]	Conservation[4]	Alternatives[5]	Mutations[6]
Val 7	✓	✓	2/7	A,T	
Ile 9	✓	✓	All		W
Gly 13	✓	✓	All		
Leu 14	✓		All		
Tyr 16	✓		All		
Ala 17	✓	✓	All		F

Ser 18	✓	✓	1/7	C,A	
Gly 21	✓	✓	All		F
Ala 24	✓	✓	4/7	V,T,S	Y,H
Leu 25	✓		All		
Ile 68	✓	✓	3/7	L	
Leu 76	✓	✓	All		
Phe 78	✓	✓	1/7	V,L	
Leu 117	✓	✓	All		
Leu 119	✓		All		
Pro 128	✓		5/7	A,S	
Ile 130	✓		1/7	V	
Val 178	✓		2/7	L,I	
Val 182	✓		All		
Glu 185	✓	✓	1/7 (allele)	K,D,H	
Leu 186	✓	✓	All		W
Tyr 189	✓	✓	All		
Phe 190	✓	✓	2/7	V,L	
Leu 193	✓	✓	All		
Leu 220	✓	✓	All		
Val 222	✓		5/7	M,W	
Val 254	✓	✓	6/7	I	
Leu 256	✓		3/7	F	
Pro 428	✓	✓	All		
Thr 429	✓	✓	1/7	M,L	
Pro 430	✓	✓	5/7	L	
Val 433	✓		3/7	I	
Leu 435	✓		All		
Val 453	✓		6/7	I	
ENTRY ONLY					
Gln 20	✓	✓	3/7	E	

Lys 27	✓	✓	3/7	R,S	
Glu 28	✓		6/7	K	
Arg 31	✓		2/7	K,E	
Ser 181	✓	✓	5/7	T,A	
Arg 432	✓	✓	3/7	K,Y,H	
Tyr 455	✓	✓	6/7	H	
C-TERMINAL POCKET - residues contributing to interior					
Phe 263	✓	✓	All		
Asn 264	✓		All		
Ala 266	✓	✓	All		F
Gly 267	✓	✓	2/7	A,S,T,	
Val 275	✓	✓	1/7	A,Y	
Leu 276	✓	✓	5/7	F,W	F,W
Lys 277	✓		1/7	G,N	
Met 278	✓	✓	1/7	L,F	
Val 318	✓		1/7	L,I,G	
Ala 320	✓		2/7	V	
Pro 324	✓	✓	6/7	Q	
Leu 326	✓	✓	6/7	V	
Phe 335	✓	✓	1/7	L,V,E	
Pro 337	✓	✓	5/7	A,F	
Val 339	✓		2/7	L,M	
Met 360	✓	✓	2/7	L,V	
Thr 362	✓	✓	5/7	L	
Val 368	✓	✓	2/7	I,L	
Leu 375	✓	✓	3/7	I,V	
Val 376	✓	✓	2/7	I,T	
Gly 377	✓		All		
Leu 379	✓	✓	All		
Leu 381	✓	✓	3/7	P	

Val 409	✓	✓	1/7	L,M,I	
Val 413	✓	✓	1/7	F,L	F
Val 417	✓	✓	3/7	I,F	W
Lys 420	✓	✓	5/7	E	Y,H
Leu 421	✓	✓	5/7	I,F	
Phe 425	✓	✓	6/7	L	
ENTRY ONLY					
Asp 200	✓		All		
Ser 201	✓	✓	4/7	K,T,N	
Val 202	✓		4/7	F,I	
Tyr 270	✓	✓	All		
Arg 416	✓	✓	1/7	K,V,D	
Lys 423	✓		3/7	R,E,Q	

[1] Residue name and number.

[2] Checked residues show a change in solvent accessible surface area with lipid binding.

[3] Checked residues have some atom within 4 Å of a lipid atom (if the contact is to the head group of the lipid, the residues are listed at the end, under **ENTRY ONLY**).

[4] Conservation in 3 BPI and 4 LBP sequences, e.g., for Ile 68, in 3 of the 7 sequences, the residue is similarly Ile; for the other 4 sequences, the residue is Leu (see note 5).

[5] Indicates alternative residues which occur in BPI or LBP at that position for the 7 BPI and LBP sequences analyzed.

[6] Indicates residues for mutations to block the pockets using residues selected to be well-conserved (especially in the N-terminal domain) and relatively small. The suggested mutations are all to large sidechains in order to decrease the size of the pocket by as much as possible.

TABLE 4

ATOM	1	CB	VAL	A	1	95.942	11.564	18.390	1.00	51.23
ATOM	2	CG1	VAL	A	1	97.217	12.313	18.805	1.00	48.90
ATOM	3	CG2	VAL	A	1	94.694	12.383	18.720	1.00	50.67
ATOM	4	C	VAL	A	1	96.124	12.502	16.083	1.00	47.46
ATOM	5	O	VAL	A	1	97.238	12.990	15.911	1.00	49.54
ATOM	8	N	VAL	A	1	97.161	10.372	16.554	1.00	51.03
ATOM	10	CA	VAL	A	1	95.982	11.216	16.876	1.00	48.79
ATOM	11	N	ASN	A	2	95.020	13.016	15.554	1.00	42.80
ATOM	13	CA	ASN	A	2	95.067	14.266	14.810	1.00	38.18
ATOM	14	CB	ASN	A	2	93.709	14.566	14.185	1.00	39.01
ATOM	15	CG	ASN	A	2	93.494	13.831	12.892	1.00	40.06
ATOM	16	OD1	ASN	A	2	94.323	13.020	12.487	1.00	42.94
ATOM	17	ND2	ASN	A	2	92.380	14.108	12.228	1.00	39.49
ATOM	20	C	ASN	A	2	95.439	15.376	15.786	1.00	34.97
ATOM	21	O	ASN	A	2	94.946	15.399	16.916	1.00	37.36
ATOM	22	N	PRO	A	3	96.373	16.260	15.397	1.00	30.80
ATOM	23	CD	PRO	A	3	97.144	16.244	14.143	1.00	28.90
ATOM	24	CA	PRO	A	3	96.806	17.367	16.252	1.00	28.19
ATOM	25	CB	PRO	A	3	98.083	17.830	15.571	1.00	26.30
ATOM	26	CG	PRO	A	3	97.765	17.619	14.128	1.00	26.17
ATOM	27	C	PRO	A	3	95.765	18.482	16.283	1.00	28.00
ATOM	28	O	PRO	A	3	95.104	18.758	15.275	1.00	28.89
ATOM	29	N	GLY	A	4	95.615	19.108	17.444	1.00	26.31
ATOM	31	CA	GLY	A	4	94.653	20.182	17.588	1.00	25.44
ATOM	32	C	GLY	A	4	95.178	21.508	17.091	1.00	25.34
ATOM	33	O	GLY	A	4	94.407	22.425	16.831	1.00	28.37
ATOM	34	N	VAL	A	5	96.494	21.621	16.981	1.00	23.98
ATOM	36	CA	VAL	A	5	97.134	22.842	16.519	1.00	21.80
ATOM	37	CB	VAL	A	5	97.671	23.681	17.689	1.00	18.63
ATOM	38	CG1	VAL	A	5	98.573	24.785	17.171	1.00	20.04
ATOM	39	CG2	VAL	A	5	96.526	24.283	18.468	1.00	20.89
ATOM	40	C	VAL	A	5	98.308	22.436	15.660	1.00	24.04
ATOM	41	O	VAL	A	5	99.014	21.486	15.984	1.00	27.65
ATOM	42	N	VAL	A	6	98.492	23.139	14.551	1.00	25.94

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ATOM	44	CA	VAL	A	6	99.589	22.874	13.633	1.00	26.54
ATOM	45	CB	VAL	A	6	99.082	22.292	12.294	1.00	29.26
ATOM	46	CG1	VAL	A	6	100.253	22.038	11.357	1.00	31.93
ATOM	47	CG2	VAL	A	6	98.318	21.001	12.535	1.00	30.52
ATOM	48	C	VAL	A	6	100.289	24.191	13.355	1.00	24.99
ATOM	49	O	VAL	A	6	99.638	25.202	13.135	1.00	26.97
ATOM	50	N	VAL	A	7	101.611	24.183	13.416	1.00	26.91
ATOM	52	CA	VAL	A	7	102.404	25.371	13.156	1.00	27.18
ATOM	53	CB	VAL	A	7	103.401	25.637	14.298	1.00	27.59
ATOM	54	CG1	VAL	A	7	104.343	26.773	13.925	1.00	27.21
ATOM	55	CG2	VAL	A	7	102.659	25.967	15.575	1.00	27.05
ATOM	56	C	VAL	A	7	103.190	25.103	11.889	1.00	29.61
ATOM	57	O	VAL	A	7	103.863	24.084	11.777	1.00	32.24
ATOM	58	N	ARG	A	8	103.077	25.994	10.917	1.00	33.04
ATOM	60	CA	ARG	A	8	103.801	25.841	9.668	1.00	33.25
ATOM	61	CB	ARG	A	8	102.842	25.631	8.494	1.00	35.70
ATOM	62	CG	ARG	A	8	102.195	24.244	8.485	1.00	41.64
ATOM	63	CD	ARG	A	8	101.309	24.004	7.259	1.00	44.24
ATOM	64	NE	ARG	A	8	102.049	23.578	6.073	1.00	48.00
ATOM	66	CZ	ARG	A	8	101.565	23.626	4.835	1.00	51.86
ATOM	67	NH1	ARG	A	8	100.341	24.091	4.611	1.00	52.72
ATOM	70	NH2	ARG	A	8	102.293	23.177	3.820	1.00	53.10
ATOM	73	C	ARG	A	8	104.682	27.052	9.441	1.00	32.06
ATOM	74	O	ARG	A	8	104.196	28.168	9.288	1.00	32.62
ATOM	75	N	ILE	A	9	105.986	26.830	9.515	1.00	31.21
ATOM	77	CA	ILE	A	9	106.955	27.888	9.315	1.00	31.97
ATOM	78	CB	ILE	A	9	108.210	27.633	10.167	1.00	32.76
ATOM	79	CG2	ILE	A	9	109.208	28.781	10.012	1.00	29.90
ATOM	80	CG1	ILE	A	9	107.803	27.454	11.633	1.00	32.76
ATOM	81	CD1	ILE	A	9	108.945	27.087	12.554	1.00	36.13
ATOM	82	C	ILE	A	9	107.309	27.889	7.832	1.00	34.24
ATOM	83	O	ILE	A	9	107.650	26.845	7.265	1.00	37.01
ATOM	84	N	SER	A	10	107.179	29.045	7.195	1.00	34.50

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ATOM	86	CA	SER	A	10	107.473	29.173	5.774	1.00	33.98
ATOM	87	CB	SER	A	10	106.536	30.200	5.146	1.00	33.86
ATOM	88	OG	SER	A	10	106.778	31.488	5.679	1.00	36.26
ATOM	90	C	SER	A	10	108.922	29.563	5.500	1.00	32.91
ATOM	91	O	SER	A	10	109.674	29.886	6.416	1.00	33.57
ATOM	92	N	GLN	A	11	109.300	29.550	4.225	1.00	34.16
ATOM	94	CA	GLN	A	11	110.653	29.912	3.811	1.00	35.54
ATOM	95	CB	GLN	A	11	110.792	29.845	2.283	1.00	35.39
ATOM	96	CG	GLN	A	11	112.212	30.070	1.746	1.00	36.23
ATOM	97	CD	GLN	A	11	113.164	28.920	2.040	1.00	35.94
ATOM	98	OE1	GLN	A	11	112.880	27.774	1.716	1.00	38.97
ATOM	99	NE2	GLN	A	11	114.310	29.230	2.624	1.00	35.28
ATOM	102	C	GLN	A	11	110.991	31.312	4.316	1.00	36.60
ATOM	103	O	GLN	A	11	112.116	31.559	4.740	1.00	41.10
ATOM	104	N	LYS	A	12	110.013	32.216	4.305	1.00	35.51
ATOM	106	CA	LYS	A	12	110.245	33.573	4.788	1.00	31.96
ATOM	107	CB	LYS	A	12	109.005	34.445	4.612	1.00	32.24
ATOM	108	CG	LYS	A	12	109.226	35.876	5.065	1.00	32.71
ATOM	109	CD	LYS	A	12	107.953	36.685	5.063	1.00	31.87
ATOM	110	CE	LYS	A	12	108.227	38.085	5.573	1.00	34.67
ATOM	111	NZ	LYS	A	12	106.998	38.914	5.627	1.00	37.88
ATOM	115	C	LYS	A	12	110.612	33.498	6.259	1.00	30.93
ATOM	116	O	LYS	A	12	111.482	34.227	6.728	1.00	32.37
ATOM	117	N	GLY	A	13	109.961	32.586	6.973	1.00	30.47
ATOM	119	CA	GLY	A	13	110.231	32.407	8.385	1.00	27.64
ATOM	120	C	GLY	A	13	111.593	31.791	8.610	1.00	29.49
ATOM	121	O	GLY	A	13	112.312	32.184	9.531	1.00	30.35
ATOM	122	N	LEU	A	14	111.952	30.817	7.779	1.00	28.87
ATOM	124	CA	LEU	A	14	113.248	30.170	7.912	1.00	28.53
ATOM	125	CB	LEU	A	14	113.361	28.941	7.011	1.00	25.60
ATOM	126	CG	LEU	A	14	112.564	27.698	7.419	1.00	25.99
ATOM	127	CD1	LEU	A	14	112.959	26.547	6.531	1.00	28.34
ATOM	128	CD2	LEU	A	14	112.829	27.330	8.855	1.00	23.90
ATOM	129	C	LEU	A	14	114.359	31.155	7.613	1.00	28.63

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ATOM	130	O	LEU	A	14	115.346	31.207	8.335	1.00	31.86
ATOM	131	N	ASP	A	15	114.176	31.972	6.582	1.00	31.30
ATOM	133	CA	ASP	A	15	115.176	32.975	6.215	1.00	33.98
ATOM	134	CB	ASP	A	15	114.695	33.832	5.033	1.00	36.03
ATOM	135	CG	ASP	A	15	114.818	33.127	3.681	1.00	36.52
ATOM	136	OD1	ASP	A	15	115.662	32.209	3.515	1.00	37.01
ATOM	137	OD2	ASP	A	15	114.071	33.530	2.765	1.00	36.25
ATOM	138	C	ASP	A	15	115.473	33.882	7.413	1.00	35.08
ATOM	139	O	ASP	A	15	116.626	34.246	7.654	1.00	37.07
ATOM	140	N	TYR	A	16	114.433	34.244	8.162	1.00	34.55
ATOM	142	CA	TYR	A	16	114.598	35.098	9.337	1.00	34.48
ATOM	143	CB	TYR	A	16	113.239	35.554	9.865	1.00	34.89
ATOM	144	CG	TYR	A	16	113.320	36.661	10.891	1.00	35.28
ATOM	145	CD1	TYR	A	16	113.859	37.905	10.562	1.00	36.36
ATOM	146	CE1	TYR	A	16	113.921	38.936	11.496	1.00	34.26
ATOM	147	CD2	TYR	A	16	112.846	36.474	12.182	1.00	33.51
ATOM	148	CE2	TYR	A	16	112.903	37.498	13.118	1.00	34.97
ATOM	149	CZ	TYR	A	16	113.440	38.724	12.767	1.00	34.08
ATOM	150	OH	TYR	A	16	113.491	39.733	13.697	1.00	37.78
ATOM	152	C	TYR	A	16	115.348	34.340	10.427	1.00	35.46
ATOM	153	O	TYR	A	16	116.240	34.883	11.074	1.00	36.90
ATOM	154	N	ALA	A	17	114.982	33.081	10.625	1.00	36.20
ATOM	156	CA	ALA	A	17	115.632	32.250	11.617	1.00	35.77
ATOM	157	CB	ALA	A	17	115.025	30.870	11.615	1.00	33.78
ATOM	158	C	ALA	A	17	117.118	32.180	11.293	1.00	37.85
ATOM	159	O	ALA	A	17	117.957	32.330	12.178	1.00	40.31
ATOM	160	N	SER	A	18	117.447	32.008	10.017	1.00	39.36
ATOM	162	CA	SER	A	18	118.846	31.927	9.612	1.00	42.40
ATOM	163	CB	SER	A	18	118.993	31.399	8.175	1.00	43.78
ATOM	164	OG	SER	A	18	118.220	32.127	7.236	1.00	48.26
ATOM	166	C	SER	A	18	119.605	33.238	9.786	1.00	42.53
ATOM	167	O	SER	A	18	120.768	33.228	10.178	1.00	44.52
ATOM	168	N	GLN	A	19	118.959	34.367	9.509	1.00	42.42

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ATOM	170	CA	GLN	A	19	119.630	35.652	9.665	1.00	42.67
ATOM	171	CB	GLN	A	19	118.805	36.806	9.089	1.00	47.13
ATOM	172	CG	GLN	A	19	118.810	36.864	7.563	1.00	57.52
ATOM	173	CD	GLN	A	19	118.457	38.238	7.012	1.00	62.74
ATOM	174	OE1	GLN	A	19	117.488	38.866	7.440	1.00	65.88
ATOM	175	NE2	GLN	A	19	119.248	38.710	6.051	1.00	64.58
ATOM	178	C	GLN	A	19	119.943	35.906	11.126	1.00	40.97
ATOM	179	O	GLN	A	19	121.030	36.378	11.456	1.00	41.85
ATOM	180	N	GLN	A	20	119.008	35.565	12.005	1.00	39.51
ATOM	182	CA	GLN	A	20	119.226	35.759	13.430	1.00	37.61
ATOM	183	CB	GLN	A	20	117.944	35.507	14.228	1.00	38.26
ATOM	184	CG	GLN	A	20	116.764	36.405	13.874	1.00	38.33
ATOM	185	CD	GLN	A	20	117.057	37.895	14.002	1.00	41.17
ATOM	186	OE1	GLN	A	20	116.912	38.642	13.040	1.00	43.42
ATOM	187	NE2	GLN	A	20	117.441	38.335	15.192	1.00	42.94
ATOM	190	C	GLN	A	20	120.325	34.805	13.878	1.00	36.56
ATOM	191	O	GLN	A	20	121.208	35.176	14.654	1.00	38.07
ATOM	192	N	GLY	A	21	120.285	33.587	13.348	1.00	36.41
ATOM	194	CA	GLY	A	21	121.276	32.585	13.688	1.00	33.84
ATOM	195	C	GLY	A	21	122.665	33.023	13.289	1.00	34.61
ATOM	196	O	GLY	A	21	123.520	33.199	14.140	1.00	36.02
ATOM	197	N	THR	A	22	122.879	33.221	11.994	1.00	35.98
ATOM	199	CA	THR	A	22	124.174	33.645	11.462	1.00	39.75
ATOM	200	CB	THR	A	22	124.036	34.109	9.983	1.00	41.34
ATOM	201	OG1	THR	A	22	123.400	33.082	9.212	1.00	40.97
ATOM	203	CG2	THR	A	22	125.397	34.408	9.377	1.00	40.54
ATOM	204	C	THR	A	22	124.780	34.785	12.285	1.00	40.46
ATOM	205	O	THR	A	22	125.954	34.741	12.667	1.00	41.11
ATOM	206	N	ALA	A	23	123.959	35.787	12.578	1.00	41.75
ATOM	208	CA	ALA	A	23	124.387	36.944	13.351	1.00	41.89
ATOM	209	CB	ALA	A	23	123.224	37.895	13.567	1.00	40.51
ATOM	210	C	ALA	A	23	124.919	36.461	14.678	1.00	43.71
ATOM	211	O	ALA	A	23	125.992	36.872	15.114	1.00	47.24
ATOM	212	N	ALA	A	24	124.175	35.554	15.298	1.00	43.71

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ATOM	214	CA	ALA	A	24	124.570	34.991	16.574	1.00	43.02
ATOM	215	CB	ALA	A	24	123.413	34.238	17.185	1.00	43.37
ATOM	216	C	ALA	A	24	125.774	34.069	16.396	1.00	42.93
ATOM	217	O	ALA	A	24	126.549	33.868	17.328	1.00	45.41
ATOM	218	N	LEU	A	25	125.944	33.532	15.193	1.00	41.61
ATOM	220	CA	LEU	A	25	127.056	32.638	14.910	1.00	40.32
ATOM	221	CB	LEU	A	25	126.746	31.755	13.699	1.00	36.89
ATOM	222	CG	LEU	A	25	127.662	30.554	13.483	1.00	34.95
ATOM	223	CD1	LEU	A	25	127.636	29.653	14.703	1.00	34.64
ATOM	224	CD2	LEU	A	25	127.218	29.797	12.262	1.00	35.16
ATOM	225	C	LEU	A	25	128.331	33.438	14.676	1.00	40.69
ATOM	226	O	LEU	A	25	129.423	32.984	15.014	1.00	42.61
ATOM	227	N	GLN	A	26	128.194	34.644	14.138	1.00	41.51
ATOM	229	CA	GLN	A	26	129.352	35.494	13.878	1.00	45.29
ATOM	230	CB	GLN	A	26	128.920	36.850	13.317	1.00	46.09
ATOM	231	CG	GLN	A	26	130.087	37.811	13.108	1.00	48.70
ATOM	232	CD	GLN	A	26	129.650	39.240	12.861	1.00	50.15
ATOM	233	OE1	GLN	A	26	129.833	40.115	13.708	1.00	51.16
ATOM	234	NE2	GLN	A	26	129.078	39.489	11.692	1.00	51.55
ATOM	237	C	GLN	A	26	130.175	35.728	15.145	1.00	46.79
ATOM	238	O	GLN	A	26	131.403	35.587	15.136	1.00	46.74
ATOM	239	N	LYS	A	27	129.488	36.081	16.230	1.00	48.40
ATOM	241	CA	LYS	A	27	130.140	36.355	17.509	1.00	50.23
ATOM	242	CB	LYS	A	27	129.119	36.696	18.595	1.00	52.58
ATOM	243	CG	LYS	A	27	128.157	37.818	18.249	1.00	55.93
ATOM	244	CD	LYS	A	27	127.495	38.391	19.503	1.00	59.98
ATOM	245	CE	LYS	A	27	126.959	37.306	20.437	1.00	63.01
ATOM	246	NZ	LYS	A	27	125.911	36.452	19.807	1.00	66.76
ATOM	250	C	LYS	A	27	130.983	35.186	17.977	1.00	50.39
ATOM	251	O	LYS	A	27	132.121	35.369	18.398	1.00	52.00
ATOM	252	N	GLU	A	28	130.421	33.984	17.920	1.00	50.09
ATOM	254	CA	GLU	A	28	131.157	32.803	18.341	1.00	48.77
ATOM	255	CB	GLU	A	28	130.250	31.571	18.390	1.00	48.51

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ATOM	256	CG	GLU	A	28	129.514	31.395	19.713	1.00	50.95
ATOM	257	CD	GLU	A	28	130.436	30.999	20.857	1.00	52.82
ATOM	258	OE1	GLU	A	28	130.687	29.789	21.030	1.00	55.51
ATOM	259	OE2	GLU	A	28	130.903	31.891	21.594	1.00	54.60
ATOM	260	C	GLU	A	28	132.343	32.564	17.421	1.00	46.96
ATOM	261	O	GLU	A	28	133.407	32.153	17.871	1.00	49.87
ATOM	262	N	LEU	A	29	132.177	32.868	16.140	1.00	43.03
ATOM	264	CA	LEU	A	29	133.257	32.674	15.189	1.00	39.75
ATOM	265	CB	LEU	A	29	132.740	32.817	13.763	1.00	36.79
ATOM	266	CG	LEU	A	29	131.832	31.658	13.360	1.00	33.73
ATOM	267	CD1	LEU	A	29	131.557	31.708	11.870	1.00	34.40
ATOM	268	CD2	LEU	A	29	132.499	30.347	13.720	1.00	31.01
ATOM	269	C	LEU	A	29	134.431	33.610	15.444	1.00	38.40
ATOM	270	O	LEU	A	29	135.584	33.204	15.348	1.00	38.06
ATOM	271	N	LYS	A	30	134.131	34.843	15.828	1.00	38.44
ATOM	273	CA	LYS	A	30	135.155	35.845	16.111	1.00	40.67
ATOM	274	CB	LYS	A	30	134.495	37.225	16.210	1.00	41.05
ATOM	275	CG	LYS	A	30	135.448	38.409	16.270	1.00	43.32
ATOM	276	CD	LYS	A	30	134.690	39.733	16.198	1.00	44.53
ATOM	277	CE	LYS	A	30	135.633	40.926	16.343	1.00	46.81
ATOM	278	NZ	LYS	A	30	134.912	42.238	16.331	1.00	50.27
ATOM	282	C	LYS	A	30	135.955	35.539	17.388	1.00	42.29
ATOM	283	O	LYS	A	30	136.979	36.166	17.654	1.00	42.94
ATOM	284	N	ARG	A	31	135.495	34.565	18.168	1.00	44.02
ATOM	286	CA	ARG	A	31	136.162	34.190	19.411	1.00	44.45
ATOM	287	CB	ARG	A	31	135.139	34.005	20.534	1.00	46.86
ATOM	288	CG	ARG	A	31	134.504	35.305	20.983	1.00	52.93
ATOM	289	CD	ARG	A	31	133.479	35.095	22.078	1.00	60.04
ATOM	290	NE	ARG	A	31	132.947	36.372	22.554	1.00	67.90
ATOM	292	CZ	ARG	A	31	131.839	36.505	23.279	1.00	71.80
ATOM	293	NH1	ARG	A	31	131.128	35.437	23.621	1.00	74.30
ATOM	296	NH2	ARG	A	31	131.444	37.710	23.672	1.00	73.67
ATOM	299	C	ARG	A	31	137.008	32.937	19.276	1.00	44.41
ATOM	300	O	ARG	A	31	137.339	32.293	20.273	1.00	46.21

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ATOM	301	N	ILE	A	32	137.343	32.581	18.041	1.00	44.30
ATOM	303	CA	ILE	A	32	138.162	31.404	17.783	1.00	42.96
ATOM	304	CB	ILE	A	32	138.054	30.953	16.308	1.00	39.50
ATOM	305	CG2	ILE	A	32	139.146	29.950	15.973	1.00	36.12
ATOM	306	CG1	ILE	A	32	136.674	30.351	16.052	1.00	37.18
ATOM	307	CD1	ILE	A	32	136.431	29.975	14.624	1.00	37.20
ATOM	308	C	ILE	A	32	139.613	31.707	18.103	1.00	44.44
ATOM	309	O	ILE	A	32	140.109	32.794	17.798	1.00	45.60
ATOM	310	N	LYS	A	33	140.288	30.747	18.725	1.00	45.45
ATOM	312	CA	LYS	A	33	141.692	30.917	19.060	1.00	46.20
ATOM	313	CB	LYS	A	33	141.958	30.569	20.522	1.00	49.33
ATOM	314	CG	LYS	A	33	141.336	31.546	21.492	1.00	52.41
ATOM	315	CD	LYS	A	33	141.910	31.387	22.885	1.00	56.15
ATOM	316	CE	LYS	A	33	143.374	31.789	22.918	1.00	59.63
ATOM	317	NZ	LYS	A	33	143.891	31.817	24.313	1.00	63.31
ATOM	321	C	LYS	A	33	142.619	30.115	18.153	1.00	44.41
ATOM	322	O	LYS	A	33	142.563	28.884	18.102	1.00	42.99
ATOM	323	N	ILE	A	34	143.442	30.836	17.408	1.00	43.49
ATOM	325	CA	ILE	A	34	144.411	30.231	16.512	1.00	43.47
ATOM	326	CB	ILE	A	34	144.452	30.958	15.159	1.00	41.93
ATOM	327	CG2	ILE	A	34	143.322	30.464	14.280	1.00	41.39
ATOM	328	CG1	ILE	A	34	144.347	32.470	15.363	1.00	42.97
ATOM	329	CD1	ILE	A	34	143.967	33.234	14.108	1.00	44.59
ATOM	330	C	ILE	A	34	145.761	30.288	17.216	1.00	44.81
ATOM	331	O	ILE	A	34	146.142	31.319	17.778	1.00	46.96
ATOM	332	N	PRO	A	35	146.464	29.151	17.267	1.00	43.85
ATOM	333	CD	PRO	A	35	146.008	27.862	16.728	1.00	44.63
ATOM	334	CA	PRO	A	35	147.773	29.003	17.904	1.00	42.65
ATOM	335	CB	PRO	A	35	148.109	27.534	17.650	1.00	42.05
ATOM	336	CG	PRO	A	35	146.778	26.887	17.578	1.00	44.72
ATOM	337	C	PRO	A	35	148.860	29.899	17.334	1.00	43.14
ATOM	338	O	PRO	A	35	148.649	30.640	16.376	1.00	44.26
ATOM	339	N	ASP	A	36	150.026	29.827	17.959	1.00	42.32

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ATOM	341	CA	ASP	A	36	151.181	30.584	17.535	1.00 41.85
ATOM	342	CB	ASP	A	36	151.933	31.125	18.745	1.00 43.04
ATOM	343	CG	ASP	A	36	151.155	32.196	19.485	1.00 45.33
ATOM	344	OD1	ASP	A	36	150.120	32.666	18.959	1.00 49.40
ATOM	345	OD2	ASP	A	36	151.591	32.584	20.588	1.00 46.99
ATOM	346	C	ASP	A	36	152.051	29.612	16.776	1.00 42.29
ATOM	347	O	ASP	A	36	152.175	28.450	17.159	1.00 43.32
ATOM	348	N	TYR	A	37	152.637	30.077	15.687	1.00 42.04
ATOM	350	CA	TYR	A	37	153.476	29.228	14.877	1.00 41.59
ATOM	351	CB	TYR	A	37	152.979	29.243	13.436	1.00 42.04
ATOM	352	CG	TYR	A	37	151.564	28.743	13.327	1.00 43.15
ATOM	353	CD1	TYR	A	37	151.295	27.378	13.256	1.00 42.32
ATOM	354	CE1	TYR	A	37	149.991	26.904	13.239	1.00 43.09
ATOM	355	CD2	TYR	A	37	150.487	29.626	13.370	1.00 44.59
ATOM	356	CE2	TYR	A	37	149.175	29.161	13.354	1.00 43.64
ATOM	357	CZ	TYR	A	37	148.938	27.799	13.291	1.00 42.12
ATOM	358	OH	TYR	A	37	147.651	27.327	13.307	1.00 43.31
ATOM	360	C	TYR	A	37	154.923	29.649	14.957	1.00 42.22
ATOM	361	O	TYR	A	37	155.311	30.692	14.443	1.00 43.15
ATOM	362	N	SER	A	38	155.714	28.833	15.634	1.00 44.23
ATOM	364	CA	SER	A	38	157.130	29.088	15.789	1.00 47.19
ATOM	365	CB	SER	A	38	157.466	29.330	17.257	1.00 47.44
ATOM	366	OG	SER	A	38	156.651	30.356	17.799	1.00 54.54
ATOM	368	C	SER	A	38	157.887	27.878	15.285	1.00 48.36
ATOM	369	O	SER	A	38	157.664	26.761	15.746	1.00 49.57
ATOM	370	N	ASP	A	39	158.773	28.103	14.327	1.00 50.18
ATOM	372	CA	ASP	A	39	159.569	27.030	13.763	1.00 52.06
ATOM	373	CB	ASP	A	39	158.822	26.402	12.579	1.00 53.01
ATOM	374	CG	ASP	A	39	159.375	25.043	12.179	1.00 54.91
ATOM	375	OD1	ASP	A	39	159.569	24.178	13.063	1.00 54.67
ATOM	376	OD2	ASP	A	39	159.600	24.837	10.969	1.00 56.72
ATOM	377	C	ASP	A	39	160.912	27.631	13.334	1.00 53.93
ATOM	378	O	ASP	A	39	161.100	28.853	13.384	1.00 54.67
ATOM	379	N	SER	A	40	161.868	26.771	13.003	1.00 54.19

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ATOM	381	CA	SER	A	40	163.187	27.208	12.577	1.00	52.94
ATOM	382	CB	SER	A	40	164.255	26.307	13.202	1.00	52.97
ATOM	383	OG	SER	A	40	163.996	24.934	12.947	1.00	53.27
ATOM	385	C	SER	A	40	163.283	27.163	11.057	1.00	54.32
ATOM	386	O	SER	A	40	162.394	26.623	10.386	1.00	54.83
ATOM	387	N	PHE	A	41	164.358	27.730	10.516	1.00	55.12
ATOM	389	CA	PHE	A	41	164.580	27.742	9.074	1.00	55.04
ATOM	390	CB	PHE	A	41	163.908	28.967	8.424	1.00	50.91
ATOM	391	CG	PHE	A	41	164.564	30.285	8.756	1.00	46.23
ATOM	392	CD1	PHE	A	41	165.720	30.695	8.092	1.00	44.94
ATOM	393	CD2	PHE	A	41	164.019	31.124	9.719	1.00	44.37
ATOM	394	CE1	PHE	A	41	166.321	31.918	8.386	1.00	43.85
ATOM	395	CE2	PHE	A	41	164.614	32.350	10.018	1.00	43.51
ATOM	396	CZ	PHE	A	41	165.765	32.746	9.351	1.00	42.57
ATOM	397	C	PHE	A	41	166.071	27.724	8.756	1.00	56.75
ATOM	398	O	PHE	A	41	166.904	27.935	9.637	1.00	58.20
ATOM	399	N	LYS	A	42	166.391	27.455	7.496	1.00	59.71
ATOM	401	CA	LYS	A	42	167.768	27.427	7.010	1.00	63.27
ATOM	402	CB	LYS	A	42	168.474	26.129	7.425	1.00	64.98
ATOM	403	CG	LYS	A	42	169.984	26.140	7.215	1.00	68.46
ATOM	404	CD	LYS	A	42	170.706	25.591	8.449	1.00	70.94
ATOM	405	CE	LYS	A	42	172.227	25.630	8.298	1.00	71.66
ATOM	406	NZ	LYS	A	42	172.928	25.300	9.582	1.00	71.11
ATOM	410	C	LYS	A	42	167.706	27.552	5.487	1.00	64.24
ATOM	411	O	LYS	A	42	167.585	26.555	4.773	1.00	65.07
ATOM	412	N	ILE	A	43	167.725	28.792	5.003	1.00	64.98
ATOM	414	CA	ILE	A	43	167.652	29.070	3.570	1.00	64.79
ATOM	415	CB	ILE	A	43	166.721	30.282	3.282	1.00	65.08
ATOM	416	CG2	ILE	A	43	166.731	30.617	1.796	1.00	66.08
ATOM	417	CG1	ILE	A	43	165.293	29.965	3.745	1.00	64.11
ATOM	418	CD1	ILE	A	43	164.284	31.071	3.478	1.00	65.50
ATOM	419	C	ILE	A	43	169.039	29.291	2.956	1.00	64.78
ATOM	420	O	ILE	A	43	169.840	30.079	3.465	1.00	65.23

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ATOM	421	N	LYS	A	44	169.273	28.631	1.825	1.00	64.51
ATOM	423	CA	LYS	A	44	170.539	28.672	1.093	1.00	63.65
ATOM	424	CB	LYS	A	44	170.328	28.232	-0.360	1.00	63.66
ATOM	425	CG	LYS	A	44	170.066	26.742	-0.553	1.00	63.81
ATOM	426	CD	LYS	A	44	170.064	26.396	-2.035	1.00	65.27
ATOM	427	CE	LYS	A	44	169.910	24.905	-2.289	1.00	65.86
ATOM	428	NZ	LYS	A	44	169.953	24.599	-3.751	1.00	66.87
ATOM	432	C	LYS	A	44	171.382	29.947	1.115	1.00	63.16
ATOM	433	O	LYS	A	44	172.600	29.876	1.274	1.00	65.20
ATOM	434	N	HIS	A	45	170.769	31.107	0.929	1.00	61.08
ATOM	436	CA	HIS	A	45	171.550	32.339	0.920	1.00	61.08
ATOM	437	CB	HIS	A	45	171.454	33.017	-0.447	1.00	64.62
ATOM	438	CG	HIS	A	45	172.039	32.214	-1.565	1.00	68.00
ATOM	439	CD2	HIS	A	45	171.695	32.126	-2.871	1.00	68.82
ATOM	440	ND1	HIS	A	45	173.124	31.380	-1.397	1.00	70.18
ATOM	442	CE1	HIS	A	45	173.425	30.815	-2.552	1.00	71.24
ATOM	443	NE2	HIS	A	45	172.572	31.250	-3.462	1.00	70.61
ATOM	445	C	HIS	A	45	171.167	33.337	1.994	1.00	59.87
ATOM	446	O	HIS	A	45	171.609	34.486	1.960	1.00	60.80
ATOM	447	N	LEU	A	46	170.345	32.900	2.940	1.00	57.18
ATOM	449	CA	LEU	A	46	169.881	33.767	4.012	1.00	53.69
ATOM	450	CB	LEU	A	46	168.362	33.699	4.103	1.00	53.23
ATOM	451	CG	LEU	A	46	167.715	34.609	5.135	1.00	51.73
ATOM	452	CD1	LEU	A	46	167.712	36.039	4.628	1.00	52.65
ATOM	453	CD2	LEU	A	46	166.310	34.126	5.390	1.00	51.01
ATOM	454	C	LEU	A	46	170.490	33.336	5.330	1.00	52.64
ATOM	455	O	LEU	A	46	170.908	34.168	6.136	1.00	52.10
ATOM	456	N	GLY	A	47	170.513	32.026	5.550	1.00	51.88
ATOM	458	CA	GLY	A	47	171.081	31.486	6.768	1.00	51.77
ATOM	459	C	GLY	A	47	170.107	30.643	7.564	1.00	51.44
ATOM	460	O	GLY	A	47	169.059	30.235	7.065	1.00	50.21
ATOM	461	N	LYS	A	48	170.484	30.357	8.802	1.00	52.15
ATOM	463	CA	LYS	A	48	169.664	29.572	9.711	1.00	52.12
ATOM	464	CB	LYS	A	48	170.497	28.479	10.407	1.00	56.73

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ATOM	465	CG	LYS	A	48	171.878	28.907	10.938	1.00	62.50
ATOM	466	CD	LYS	A	48	172.953	28.876	9.843	1.00	65.46
ATOM	467	CE	LYS	A	48	174.332	29.252	10.380	1.00	66.23
ATOM	468	NZ	LYS	A	48	175.380	29.178	9.318	1.00	65.64
ATOM	472	C	LYS	A	48	169.041	30.510	10.738	1.00	49.63
ATOM	473	O	LYS	A	48	169.632	31.533	11.101	1.00	48.85
ATOM	474	N	GLY	A	49	167.846	30.174	11.200	1.00	46.79
ATOM	476	CA	GLY	A	49	167.197	31.026	12.169	1.00	47.22
ATOM	477	C	GLY	A	49	165.918	30.449	12.728	1.00	47.47
ATOM	478	O	GLY	A	49	165.594	29.285	12.506	1.00	46.51
ATOM	479	N	HIS	A	50	165.166	31.292	13.420	1.00	47.82
ATOM	481	CA	HIS	A	50	163.922	30.886	14.041	1.00	48.80
ATOM	482	CB	HIS	A	50	164.126	30.793	15.554	1.00	58.27
ATOM	483	CG	HIS	A	50	163.658	29.505	16.155	1.00	68.69
ATOM	484	CD2	HIS	A	50	164.349	28.453	16.657	1.00	72.98
ATOM	485	ND1	HIS	A	50	162.324	29.196	16.311	1.00	73.69
ATOM	487	CE1	HIS	A	50	162.212	28.010	16.885	1.00	76.58
ATOM	488	NE2	HIS	A	50	163.426	27.539	17.105	1.00	77.46
ATOM	490	C	HIS	A	50	162.905	31.965	13.742	1.00	45.89
ATOM	491	O	HIS	A	50	163.149	33.137	14.019	1.00	41.84
ATOM	492	N	TYR	A	51	161.785	31.585	13.143	1.00	46.60
ATOM	494	CA	TYR	A	51	160.746	32.555	12.824	1.00	48.52
ATOM	495	CB	TYR	A	51	160.308	32.420	11.354	1.00	50.04
ATOM	496	CG	TYR	A	51	159.360	31.280	11.098	1.00	51.79
ATOM	497	CD1	TYR	A	51	157.987	31.449	11.266	1.00	53.21
ATOM	498	CE1	TYR	A	51	157.111	30.396	11.103	1.00	56.71
ATOM	499	CD2	TYR	A	51	159.833	30.021	10.745	1.00	52.56
ATOM	500	CE2	TYR	A	51	158.959	28.955	10.573	1.00	56.44
ATOM	501	CZ	TYR	A	51	157.597	29.149	10.761	1.00	58.01
ATOM	502	OH	TYR	A	51	156.717	28.094	10.649	1.00	60.76
ATOM	504	C	TYR	A	51	159.566	32.330	13.763	1.00	47.31
ATOM	505	O	TYR	A	51	159.485	31.291	14.424	1.00	47.36
ATOM	506	N	SER	A	52	158.648	33.288	13.812	1.00	46.53

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ATOM	508	CA	SER	A	52	157.480	33.163	14.669	1.00	43.69
ATOM	509	CB	SER	A	52	157.862	33.449	16.123	1.00	43.87
ATOM	510	OG	SER	A	52	156.759	33.233	16.986	1.00	42.88
ATOM	512	C	SER	A	52	156.344	34.083	14.253	1.00	41.60
ATOM	513	O	SER	A	52	156.558	35.261	13.981	1.00	42.86
ATOM	514	N	PHE	A	53	155.152	33.513	14.132	1.00	39.20
ATOM	516	CA	PHE	A	53	153.944	34.260	13.796	1.00	36.73
ATOM	517	CB	PHE	A	53	153.310	33.737	12.507	1.00	33.91
ATOM	518	CG	PHE	A	53	154.107	34.054	11.271	1.00	32.26
ATOM	519	CD1	PHE	A	53	154.039	35.311	10.691	1.00	31.58
ATOM	520	CD2	PHE	A	53	154.912	33.092	10.682	1.00	30.53
ATOM	521	CE1	PHE	A	53	154.759	35.603	9.545	1.00	30.85
ATOM	522	CE2	PHE	A	53	155.637	33.373	9.533	1.00	30.45
ATOM	523	CZ	PHE	A	53	155.559	34.631	8.964	1.00	30.49
ATOM	524	C	PHE	A	53	153.071	33.965	15.006	1.00	35.40
ATOM	525	O	PHE	A	53	152.746	32.814	15.276	1.00	34.75
ATOM	526	N	TYR	A	54	152.720	34.998	15.757	1.00	34.80
ATOM	528	CA	TYR	A	54	151.960	34.798	16.974	1.00	37.29
ATOM	529	CB	TYR	A	54	152.947	34.533	18.103	1.00	39.38
ATOM	530	CG	TYR	A	54	153.841	35.721	18.375	1.00	42.01
ATOM	531	CD1	TYR	A	54	154.782	36.139	17.437	1.00	42.10
ATOM	532	CE1	TYR	A	54	155.552	37.270	17.649	1.00	40.85
ATOM	533	CD2	TYR	A	54	153.703	36.467	19.541	1.00	43.83
ATOM	534	CE2	TYR	A	54	154.472	37.600	19.763	1.00	43.33
ATOM	535	CZ	TYR	A	54	155.391	37.995	18.811	1.00	42.17
ATOM	536	OH	TYR	A	54	156.139	39.126	19.018	1.00	46.33
ATOM	538	C	TYR	A	54	151.100	35.990	17.362	1.00	38.69
ATOM	539	O	TYR	A	54	151.072	37.007	16.672	1.00	41.66
ATOM	540	N	SER	A	55	150.430	35.858	18.505	1.00	40.04
ATOM	542	CA	SER	A	55	149.562	36.894	19.056	1.00	40.41
ATOM	543	CB	SER	A	55	150.407	38.091	19.499	1.00	41.89
ATOM	544	OG	SER	A	55	149.708	38.923	20.409	1.00	46.68
ATOM	546	C	SER	A	55	148.489	37.318	18.051	1.00	41.35
ATOM	547	O	SER	A	55	148.115	38.492	17.973	1.00	40.80

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ATOM	548	N	MET	A	56	147.984	36.346	17.299	1.00	42.39
ATOM	550	CA	MET	A	56	146.968	36.606	16.292	1.00	43.64
ATOM	551	CB	MET	A	56	146.996	35.513	15.225	1.00	42.07
ATOM	552	CG	MET	A	56	148.310	35.414	14.475	1.00	39.09
ATOM	553	SD	MET	A	56	148.335	34.056	13.289	1.00	41.60
ATOM	554	CE	MET	A	56	149.266	32.847	14.209	1.00	36.68
ATOM	555	C	MET	A	56	145.580	36.708	16.910	1.00	46.06
ATOM	556	O	MET	A	56	145.222	35.928	17.794	1.00	48.27
ATOM	557	N	ASP	A	57	144.820	37.700	16.463	1.00	47.20
ATOM	559	CA	ASP	A	57	143.466	37.930	16.941	1.00	47.94
ATOM	560	CB	ASP	A	57	143.408	39.167	17.848	1.00	52.70
ATOM	561	CG	ASP	A	57	143.578	38.831	19.324	1.00	58.73
ATOM	562	OD1	ASP	A	57	142.552	38.587	19.999	1.00	62.99
ATOM	563	OD2	ASP	A	57	144.729	38.835	19.818	1.00	59.77
ATOM	564	C	ASP	A	57	142.566	38.151	15.736	1.00	46.86
ATOM	565	O	ASP	A	57	143.001	38.684	14.712	1.00	44.98
ATOM	566	N	ILE	A	58	141.324	37.699	15.843	1.00	45.46
ATOM	568	CA	ILE	A	58	140.356	37.872	14.773	1.00	45.28
ATOM	569	CB	ILE	A	58	139.232	36.822	14.869	1.00	42.99
ATOM	570	CG2	ILE	A	58	138.200	37.052	13.782	1.00	41.93
ATOM	571	CG1	ILE	A	58	139.825	35.415	14.744	1.00	42.15
ATOM	572	CD1	ILE	A	58	138.803	34.306	14.802	1.00	41.09
ATOM	573	C	ILE	A	58	139.783	39.277	14.936	1.00	47.07
ATOM	574	O	ILE	A	58	139.271	39.615	15.999	1.00	48.46
ATOM	575	N	ARG	A	59	139.945	40.116	13.918	1.00	49.05
ATOM	577	CA	ARG	A	59	139.441	41.486	13.973	1.00	51.28
ATOM	578	CB	ARG	A	59	140.435	42.459	13.326	1.00	53.21
ATOM	579	CG	ARG	A	59	141.760	42.590	14.062	1.00	55.13
ATOM	580	CD	ARG	A	59	141.578	43.175	15.453	1.00	59.25
ATOM	581	NE	ARG	A	59	142.833	43.178	16.202	1.00	63.13
ATOM	583	CZ	ARG	A	59	142.981	43.681	17.424	1.00	66.00
ATOM	584	NH1	ARG	A	59	141.950	44.231	18.054	1.00	68.47
ATOM	587	NH2	ARG	A	59	144.164	43.631	18.022	1.00	67.15

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ATOM	590	C	ARG	A	59	138.066	41.627	13.322	1.00	52.12
ATOM	591	O	ARG	A	59	137.256	42.456	13.746	1.00	54.45
ATOM	592	N	GLU	A	60	137.823	40.857	12.265	1.00	52.91
ATOM	594	CA	GLU	A	60	136.538	40.878	11.570	1.00	52.94
ATOM	595	CB	GLU	A	60	136.492	41.944	10.476	1.00	55.28
ATOM	596	CG	GLU	A	60	135.133	41.994	9.776	1.00	60.74
ATOM	597	CD	GLU	A	60	135.131	42.841	8.523	1.00	64.33
ATOM	598	OE1	GLU	A	60	135.450	44.046	8.618	1.00	67.37
ATOM	599	OE2	GLU	A	60	134.798	42.300	7.443	1.00	65.16
ATOM	600	C	GLU	A	60	136.279	39.518	10.948	1.00	51.42
ATOM	601	O	GLU	A	60	137.170	38.930	10.342	1.00	52.44
ATOM	602	N	PHE	A	61	135.052	39.035	11.093	1.00	50.66
ATOM	604	CA	PHE	A	61	134.646	37.741	10.558	1.00	49.14
ATOM	605	CB	PHE	A	61	134.536	36.736	11.707	1.00	44.10
ATOM	606	CG	PHE	A	61	134.679	35.308	11.289	1.00	37.41
ATOM	607	CD1	PHE	A	61	133.998	34.814	10.188	1.00	36.68
ATOM	608	CD2	PHE	A	61	135.486	34.448	12.018	1.00	34.73
ATOM	609	CE1	PHE	A	61	134.116	33.477	9.817	1.00	36.53
ATOM	610	CE2	PHE	A	61	135.612	33.115	11.658	1.00	34.86
ATOM	611	CZ	PHE	A	61	134.922	32.627	10.553	1.00	35.68
ATOM	612	C	PHE	A	61	133.278	37.962	9.924	1.00	50.95
ATOM	613	O	PHE	A	61	132.249	37.646	10.521	1.00	52.86
ATOM	614	N	GLN	A	62	133.259	38.540	8.729	1.00	51.57
ATOM	616	CA	GLN	A	62	131.993	38.813	8.080	1.00	51.07
ATOM	617	CB	GLN	A	62	132.097	39.993	7.120	1.00	54.59
ATOM	618	CG	GLN	A	62	130.727	40.463	6.639	1.00	62.31
ATOM	619	CD	GLN	A	62	130.775	41.665	5.708	1.00	67.35
ATOM	620	OE1	GLN	A	62	129.812	41.935	4.991	1.00	69.86
ATOM	621	NE2	GLN	A	62	131.884	42.401	5.727	1.00	71.01
ATOM	624	C	GLN	A	62	131.391	37.625	7.367	1.00	48.52
ATOM	625	O	GLN	A	62	132.065	36.912	6.629	1.00	48.13
ATOM	626	N	LEU	A	63	130.107	37.422	7.622	1.00	48.11
ATOM	628	CA	LEU	A	63	129.324	36.358	7.017	1.00	47.47
ATOM	629	CB	LEU	A	63	128.753	35.438	8.103	1.00	44.43

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ATOM	630	CG	LEU	A	63	129.754	34.759	9.044	1.00	42.13
ATOM	631	CD1	LEU	A	63	129.021	34.080	10.181	1.00	42.20
ATOM	632	CD2	LEU	A	63	130.593	33.752	8.282	1.00	40.96
ATOM	633	C	LEU	A	63	128.208	37.122	6.314	1.00	48.35
ATOM	634	O	LEU	A	63	127.138	37.345	6.882	1.00	49.30
ATOM	635	N	PRO	A	64	128.471	37.585	5.082	1.00	49.75
ATOM	636	CD	PRO	A	64	129.686	37.302	4.297	1.00	50.27
ATOM	637	CA	PRO	A	64	127.508	38.347	4.283	1.00	50.73
ATOM	638	CB	PRO	A	64	128.309	38.687	3.026	1.00	50.48
ATOM	639	CG	PRO	A	64	129.210	37.513	2.878	1.00	49.49
ATOM	640	C	PRO	A	64	126.219	37.616	3.937	1.00	51.98
ATOM	641	O	PRO	A	64	125.129	38.167	4.083	1.00	54.28
ATOM	642	N	SER	A	65	126.341	36.375	3.488	1.00	51.59
ATOM	644	CA	SER	A	65	125.177	35.607	3.101	1.00	50.95
ATOM	645	CB	SER	A	65	125.217	35.356	1.599	1.00	52.70
ATOM	646	OG	SER	A	65	126.503	34.910	1.205	1.00	55.07
ATOM	648	C	SER	A	65	125.053	34.288	3.832	1.00	50.87
ATOM	649	O	SER	A	65	126.052	33.627	4.120	1.00	52.05
ATOM	650	N	SER	A	66	123.811	33.928	4.136	1.00	50.53
ATOM	652	CA	SER	A	66	123.477	32.680	4.805	1.00	48.85
ATOM	653	CB	SER	A	66	123.322	32.878	6.312	1.00	48.24
ATOM	654	OG	SER	A	66	122.307	33.820	6.615	1.00	49.82
ATOM	656	C	SER	A	66	122.154	32.244	4.202	1.00	49.43
ATOM	657	O	SER	A	66	121.365	33.080	3.745	1.00	48.59
ATOM	658	N	GLN	A	67	121.925	30.940	4.165	1.00	49.88
ATOM	660	CA	GLN	A	67	120.696	30.409	3.605	1.00	49.90
ATOM	661	CB	GLN	A	67	120.831	30.267	2.086	1.00	52.61
ATOM	662	CG	GLN	A	67	121.928	29.308	1.632	1.00	58.79
ATOM	663	CD	GLN	A	67	121.984	29.154	0.121	1.00	62.57
ATOM	664	OE1	GLN	A	67	122.550	29.997	-0.576	1.00	66.32
ATOM	665	NE2	GLN	A	67	121.407	28.073	-0.392	1.00	62.89
ATOM	668	C	GLN	A	67	120.337	29.065	4.221	1.00	48.02
ATOM	669	O	GLN	A	67	121.215	28.306	4.635	1.00	49.44

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ATOM	670	N	ILE	A	68	119.040	28.803	4.328	1.00	45.23
ATOM	672	CA	ILE	A	68	118.551	27.544	4.864	1.00	42.63
ATOM	673	CB	ILE	A	68	117.826	27.721	6.220	1.00	44.01
ATOM	674	CG2	ILE	A	68	116.977	26.499	6.546	1.00	45.24
ATOM	675	CG1	ILE	A	68	118.850	27.925	7.333	1.00	44.56
ATOM	676	CD1	ILE	A	68	118.260	27.851	8.719	1.00	47.20
ATOM	677	C	ILE	A	68	117.613	26.935	3.835	1.00	40.01
ATOM	678	O	ILE	A	68	116.560	27.491	3.524	1.00	41.30
ATOM	679	N	SER	A	69	118.051	25.833	3.250	1.00	37.17
ATOM	681	CA	SER	A	69	117.264	25.140	2.258	1.00	34.46
ATOM	682	CB	SER	A	69	118.165	24.600	1.147	1.00	34.89
ATOM	683	OG	SER	A	69	118.890	25.640	0.511	1.00	40.63
ATOM	685	C	SER	A	69	116.570	23.984	2.939	1.00	33.71
ATOM	686	O	SER	A	69	117.085	23.414	3.896	1.00	34.03
ATOM	687	N	MET	A	70	115.405	23.625	2.430	1.00	33.11
ATOM	689	CA	MET	A	70	114.659	22.519	2.981	1.00	34.74
ATOM	690	CB	MET	A	70	113.166	22.841	3.012	1.00	36.59
ATOM	691	CG	MET	A	70	112.794	23.880	4.051	1.00	41.38
ATOM	692	SD	MET	A	70	111.050	24.288	4.028	1.00	47.62
ATOM	693	CE	MET	A	70	111.101	25.834	3.173	1.00	47.72
ATOM	694	C	MET	A	70	114.906	21.274	2.153	1.00	35.74
ATOM	695	O	MET	A	70	114.752	21.279	0.928	1.00	37.33
ATOM	696	N	VAL	A	71	115.366	20.226	2.820	1.00	35.02
ATOM	698	CA	VAL	A	71	115.613	18.957	2.165	1.00	32.82
ATOM	699	CB	VAL	A	71	116.938	18.343	2.637	1.00	30.47
ATOM	700	CG1	VAL	A	71	117.206	17.049	1.905	1.00	28.06
ATOM	701	CG2	VAL	A	71	118.069	19.324	2.404	1.00	28.88
ATOM	702	C	VAL	A	71	114.438	18.072	2.571	1.00	33.73
ATOM	703	O	VAL	A	71	114.430	17.505	3.664	1.00	35.31
ATOM	704	N	PRO	A	72	113.411	17.975	1.708	1.00	33.98
ATOM	705	CD	PRO	A	72	113.402	18.500	0.327	1.00	33.44
ATOM	706	CA	PRO	A	72	112.211	17.168	1.965	1.00	34.72
ATOM	707	CB	PRO	A	72	111.660	16.936	0.562	1.00	33.90
ATOM	708	CG	PRO	A	72	111.980	18.231	-0.124	1.00	32.49

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ATOM	709	C	PRO	A	72	112.495	15.857	2.695	1.00	36.34
ATOM	710	O	PRO	A	72	113.417	15.131	2.340	1.00	39.70
ATOM	711	N	ASN	A	73	111.745	15.607	3.765	1.00	38.08
ATOM	713	CA	ASN	A	73	111.886	14.399	4.580	1.00	39.44
ATOM	714	CB	ASN	A	73	111.553	13.146	3.768	1.00	45.34
ATOM	715	CG	ASN	A	73	110.071	12.875	3.699	1.00	50.49
ATOM	716	OD1	ASN	A	73	109.392	13.317	2.770	1.00	53.54
ATOM	717	ND2	ASN	A	73	109.552	12.149	4.690	1.00	53.95
ATOM	720	C	ASN	A	73	113.231	14.192	5.252	1.00	38.00
ATOM	721	O	ASN	A	73	113.408	13.204	5.962	1.00	37.89
ATOM	722	N	VAL	A	74	114.165	15.116	5.050	1.00	37.67
ATOM	724	CA	VAL	A	74	115.498	14.995	5.632	1.00	36.66
ATOM	725	CB	VAL	A	74	116.598	15.041	4.525	1.00	37.47
ATOM	726	CG1	VAL	A	74	117.976	14.753	5.118	1.00	35.10
ATOM	727	CG2	VAL	A	74	116.280	14.046	3.402	1.00	33.69
ATOM	728	C	VAL	A	74	115.784	16.054	6.704	1.00	37.30
ATOM	729	O	VAL	A	74	116.106	15.717	7.848	1.00	39.11
ATOM	730	N	GLY	A	75	115.672	17.328	6.342	1.00	35.75
ATOM	732	CA	GLY	A	75	115.928	18.384	7.306	1.00	33.77
ATOM	733	C	GLY	A	75	116.279	19.698	6.647	1.00	33.37
ATOM	734	O	GLY	A	75	115.827	19.981	5.536	1.00	32.85
ATOM	735	N	LEU	A	76	117.075	20.509	7.338	1.00	34.22
ATOM	737	CA	LEU	A	76	117.504	21.811	6.828	1.00	33.33
ATOM	738	CB	LEU	A	76	117.329	22.894	7.897	1.00	30.43
ATOM	739	CG	LEU	A	76	115.958	23.105	8.524	1.00	28.67
ATOM	740	CD1	LEU	A	76	116.081	24.069	9.683	1.00	29.06
ATOM	741	CD2	LEU	A	76	114.995	23.633	7.481	1.00	31.34
ATOM	742	C	LEU	A	76	118.979	21.755	6.448	1.00	33.33
ATOM	743	O	LEU	A	76	119.736	20.942	6.967	1.00	34.06
ATOM	744	N	LYS	A	77	119.383	22.636	5.550	1.00	34.34
ATOM	746	CA	LYS	A	77	120.766	22.711	5.131	1.00	33.56
ATOM	747	CB	LYS	A	77	120.927	22.201	3.700	1.00	35.32
ATOM	748	CG	LYS	A	77	122.345	22.283	3.166	1.00	38.99

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ATOM	749	CD	LYS	A	77	122.450	21.670	1.782	1.00	41.42
ATOM	750	CE	LYS	A	77	122.388	20.150	1.838	1.00	41.64
ATOM	751	NZ	LYS	A	77	123.630	19.565	2.421	1.00	43.94
ATOM	755	C	LYS	A	77	121.131	24.175	5.228	1.00	34.11
ATOM	756	O	LYS	A	77	120.556	25.013	4.538	1.00	34.01
ATOM	757	N	PHE	A	78	122.009	24.478	6.173	1.00	36.93
ATOM	759	CA	PHE	A	78	122.482	25.830	6.427	1.00	37.23
ATOM	760	CB	PHE	A	78	122.720	25.983	7.933	1.00	37.11
ATOM	761	CG	PHE	A	78	123.233	27.329	8.340	1.00	36.19
ATOM	762	CD1	PHE	A	78	122.536	28.481	8.016	1.00	35.10
ATOM	763	CD2	PHE	A	78	124.415	27.442	9.059	1.00	36.97
ATOM	764	CE1	PHE	A	78	123.008	29.725	8.400	1.00	33.97
ATOM	765	CE2	PHE	A	78	124.892	28.679	9.446	1.00	36.53
ATOM	766	CZ	PHE	A	78	124.185	29.824	9.115	1.00	36.23
ATOM	767	C	PHE	A	78	123.780	26.063	5.646	1.00	38.21
ATOM	768	O	PHE	A	78	124.706	25.256	5.731	1.00	37.35
ATOM	769	N	SER	A	79	123.845	27.160	4.892	1.00	39.48
ATOM	771	CA	SER	A	79	125.028	27.489	4.097	1.00	40.20
ATOM	772	CB	SER	A	79	124.802	27.126	2.625	1.00	41.51
ATOM	773	OG	SER	A	79	124.408	25.773	2.464	1.00	48.40
ATOM	775	C	SER	A	79	125.416	28.963	4.160	1.00	40.10
ATOM	776	O	SER	A	79	124.557	29.842	4.112	1.00	39.14
ATOM	777	N	ILE	A	80	126.713	29.219	4.297	1.00	40.97
ATOM	779	CA	ILE	A	80	127.263	30.575	4.309	1.00	41.40
ATOM	780	CB	ILE	A	80	128.002	30.885	5.612	1.00	39.45
ATOM	781	CG2	ILE	A	80	128.518	32.307	5.583	1.00	40.67
ATOM	782	CG1	ILE	A	80	127.057	30.714	6.797	1.00	38.41
ATOM	783	CD1	ILE	A	80	127.690	31.022	8.120	1.00	39.45
ATOM	784	C	ILE	A	80	128.246	30.524	3.143	1.00	43.93
ATOM	785	O	ILE	A	80	128.944	29.519	2.976	1.00	45.50
ATOM	786	N	SER	A	81	128.327	31.585	2.344	1.00	47.35
ATOM	788	CA	SER	A	81	129.193	31.541	1.168	1.00	49.22
ATOM	789	CB	SER	A	81	128.338	31.613	-0.097	1.00	49.49
ATOM	790	OG	SER	A	81	127.332	32.602	0.032	1.00	52.43

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ATOM	792	C	SER	A	81	130.412	32.432	1.004	1.00	50.65
ATOM	793	O	SER	A	81	131.482	31.937	0.658	1.00	52.88
ATOM	794	N	ASN	A	82	130.276	33.738	1.185	1.00	52.50
ATOM	796	CA	ASN	A	82	131.442	34.599	0.995	1.00	54.71
ATOM	797	CB	ASN	A	82	131.104	35.767	0.061	1.00	58.34
ATOM	798	CG	ASN	A	82	132.342	36.391	-0.570	1.00	61.43
ATOM	799	OD1	ASN	A	82	132.462	37.613	-0.657	1.00	63.94
ATOM	800	ND2	ASN	A	82	133.257	35.550	-1.039	1.00	61.92
ATOM	803	C	ASN	A	82	132.040	35.098	2.303	1.00	54.00
ATOM	804	O	ASN	A	82	132.268	36.297	2.482	1.00	54.15
ATOM	805	N	ALA	A	83	132.325	34.162	3.205	1.00	53.37
ATOM	807	CA	ALA	A	83	132.892	34.501	4.506	1.00	52.11
ATOM	808	CB	ALA	A	83	132.952	33.273	5.402	1.00	51.81
ATOM	809	C	ALA	A	83	134.272	35.131	4.359	1.00	50.64
ATOM	810	O	ALA	A	83	135.124	34.640	3.610	1.00	49.58
ATOM	811	N	ASN	A	84	134.467	36.228	5.078	1.00	48.85
ATOM	813	CA	ASN	A	84	135.706	36.983	5.063	1.00	47.97
ATOM	814	CB	ASN	A	84	135.423	38.393	4.536	1.00	51.32
ATOM	815	CG	ASN	A	84	136.560	39.361	4.793	1.00	56.05
ATOM	816	OD1	ASN	A	84	137.470	39.499	3.978	1.00	61.24
ATOM	817	ND2	ASN	A	84	136.500	40.060	5.919	1.00	56.91
ATOM	820	C	ASN	A	84	136.243	37.042	6.485	1.00	45.82
ATOM	821	O	ASN	A	84	135.601	37.606	7.368	1.00	47.29
ATOM	822	N	ILE	A	85	137.405	36.438	6.703	1.00	43.85
ATOM	824	CA	ILE	A	85	138.052	36.402	8.014	1.00	41.41
ATOM	825	CB	ILE	A	85	138.495	34.952	8.386	1.00	35.61
ATOM	826	CG2	ILE	A	85	139.011	34.901	9.804	1.00	32.01
ATOM	827	CG1	ILE	A	85	137.342	33.965	8.222	1.00	30.72
ATOM	828	CD1	ILE	A	85	137.712	32.557	8.587	1.00	25.79
ATOM	829	C	ILE	A	85	139.315	37.272	8.017	1.00	43.73
ATOM	830	O	ILE	A	85	140.343	36.873	7.471	1.00	47.66
ATOM	831	N	LYS	A	86	139.239	38.471	8.578	1.00	42.83
ATOM	833	CA	LYS	A	86	140.420	39.313	8.645	1.00	43.65

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ATOM	834	CB	LYS	A	86	140.090	40.779	8.363	1.00	47.39
ATOM	835	CG	LYS	A	86	139.895	41.055	6.873	1.00	54.31
ATOM	836	CD	LYS	A	86	140.065	42.528	6.509	1.00	58.05
ATOM	837	CE	LYS	A	86	138.937	43.394	7.045	1.00	61.18
ATOM	838	NZ	LYS	A	86	139.107	44.820	6.642	1.00	64.32
ATOM	842	C	LYS	A	86	141.100	39.135	9.996	1.00	43.61
ATOM	843	O	LYS	A	86	140.514	39.404	11.043	1.00	42.95
ATOM	844	N	ILE	A	87	142.327	38.627	9.961	1.00	43.89
ATOM	846	CA	ILE	A	87	143.104	38.373	11.165	1.00	44.27
ATOM	847	CB	ILE	A	87	143.568	36.895	11.206	1.00	43.55
ATOM	848	CG2	ILE	A	87	144.365	36.609	12.473	1.00	42.71
ATOM	849	CG1	ILE	A	87	142.358	35.964	11.129	1.00	41.65
ATOM	850	CD1	ILE	A	87	142.723	34.504	11.044	1.00	42.75
ATOM	851	C	ILE	A	87	144.327	39.291	11.212	1.00	44.82
ATOM	852	O	ILE	A	87	144.817	39.745	10.176	1.00	46.46
ATOM	853	N	SER	A	88	144.805	39.568	12.417	1.00	43.43
ATOM	855	CA	SER	A	88	145.970	40.414	12.606	1.00	44.37
ATOM	856	CB	SER	A	88	145.548	41.825	13.027	1.00	46.30
ATOM	857	OG	SER	A	88	144.757	42.451	12.029	1.00	50.16
ATOM	859	C	SER	A	88	146.830	39.795	13.690	1.00	43.85
ATOM	860	O	SER	A	88	146.327	39.073	14.549	1.00	43.41
ATOM	861	N	GLY	A	89	148.128	40.061	13.638	1.00	45.04
ATOM	863	CA	GLY	A	89	149.029	39.525	14.640	1.00	47.03
ATOM	864	C	GLY	A	89	150.415	40.123	14.532	1.00	47.50
ATOM	865	O	GLY	A	89	150.611	41.140	13.861	1.00	47.81
ATOM	866	N	LYS	A	90	151.377	39.497	15.200	1.00	47.62
ATOM	868	CA	LYS	A	90	152.759	39.957	15.176	1.00	47.17
ATOM	869	CB	LYS	A	90	153.197	40.427	16.567	1.00	47.20
ATOM	870	CG	LYS	A	90	152.328	41.514	17.189	1.00	49.57
ATOM	871	CD	LYS	A	90	152.708	41.723	18.651	1.00	53.99
ATOM	872	CE	LYS	A	90	151.725	42.625	19.391	1.00	57.45
ATOM	873	NZ	LYS	A	90	152.042	42.735	20.855	1.00	59.91
ATOM	877	C	LYS	A	90	153.629	38.787	14.738	1.00	45.69
ATOM	878	O	LYS	A	90	153.171	37.644	14.697	1.00	45.87

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ATOM	879	N	TRP	A	91	154.874	39.078	14.389	1.00	44.12
ATOM	881	CA	TRP	A	91	155.817	38.052	13.969	1.00	43.19
ATOM	882	CB	TRP	A	91	155.734	37.824	12.456	1.00	39.90
ATOM	883	CG	TRP	A	91	156.078	39.038	11.694	1.00	37.85
ATOM	884	CD2	TRP	A	91	157.390	39.466	11.313	1.00	39.20
ATOM	885	CE2	TRP	A	91	157.251	40.722	10.682	1.00	39.17
ATOM	886	CE3	TRP	A	91	158.672	38.918	11.451	1.00	36.54
ATOM	887	CD1	TRP	A	91	155.222	40.012	11.286	1.00	39.46
ATOM	888	NE1	TRP	A	91	155.916	41.032	10.681	1.00	39.30
ATOM	890	CZ2	TRP	A	91	158.344	41.437	10.188	1.00	38.03
ATOM	891	CZ3	TRP	A	91	159.757	39.628	10.963	1.00	35.59
ATOM	892	CH2	TRP	A	91	159.585	40.876	10.338	1.00	36.22
ATOM	893	C	TRP	A	91	157.218	38.520	14.339	1.00	43.43
ATOM	894	O	TRP	A	91	157.460	39.717	14.509	1.00	44.14
ATOM	895	N	LYS	A	92	158.136	37.575	14.468	1.00	44.32
ATOM	897	CA	LYS	A	92	159.517	37.892	14.789	1.00	44.34
ATOM	898	CB	LYS	A	92	159.717	38.076	16.302	1.00	47.57
ATOM	899	CG	LYS	A	92	159.252	36.933	17.200	1.00	53.21
ATOM	900	CD	LYS	A	92	159.361	37.354	18.678	1.00	57.24
ATOM	901	CE	LYS	A	92	158.844	36.283	19.650	1.00	59.23
ATOM	902	NZ	LYS	A	92	158.816	36.742	21.083	1.00	59.30
ATOM	906	C	LYS	A	92	160.409	36.801	14.227	1.00	42.18
ATOM	907	O	LYS	A	92	160.052	35.623	14.255	1.00	43.11
ATOM	908	N	ALA	A	93	161.521	37.214	13.632	1.00	39.24
ATOM	910	CA	ALA	A	93	162.471	36.294	13.033	1.00	36.99
ATOM	911	CB	ALA	A	93	162.410	36.392	11.515	1.00	36.10
ATOM	912	C	ALA	A	93	163.850	36.675	13.525	1.00	37.81
ATOM	913	O	ALA	A	93	164.130	37.851	13.747	1.00	39.61
ATOM	914	N	GLN	A	94	164.706	35.679	13.705	1.00	39.81
ATOM	916	CA	GLN	A	94	166.060	35.919	14.173	1.00	41.70
ATOM	917	CB	GLN	A	94	166.184	35.541	15.647	1.00	45.63
ATOM	918	CG	GLN	A	94	167.552	35.803	16.237	1.00	55.83
ATOM	919	CD	GLN	A	94	167.559	35.745	17.750	1.00	63.01

SUBSTITUTE SHEET (RULE 26)

ATOM	920	OE1	GLN	A	94	168.328	36.456	18.406	1.00	67.41
ATOM	921	NE2	GLN	A	94	166.703	34.899	18.320	1.00	66.99
ATOM	924	C	GLN	A	94	167.067	35.139	13.340	1.00	41.13
ATOM	925	O	GLN	A	94	166.952	33.921	13.194	1.00	41.48
ATOM	926	N	LYS	A	95	168.024	35.865	12.771	1.00	41.51
ATOM	928	CA	LYS	A	95	169.084	35.302	11.938	1.00	40.50
ATOM	929	CB	LYS	A	95	169.000	35.901	10.531	1.00	40.86
ATOM	930	CG	LYS	A	95	170.099	35.478	9.580	1.00	44.00
ATOM	931	CD	LYS	A	95	169.849	36.030	8.175	1.00	46.44
ATOM	932	CE	LYS	A	95	169.767	37.553	8.161	1.00	48.82
ATOM	933	NZ	LYS	A	95	169.529	38.117	6.799	1.00	49.76
ATOM	937	C	LYS	A	95	170.381	35.705	12.631	1.00	39.51
ATOM	938	O	LYS	A	95	170.781	36.869	12.594	1.00	39.68
ATOM	939	N	ARG	A	96	171.000	34.743	13.304	1.00	39.70
ATOM	941	CA	ARG	A	96	172.229	34.965	14.065	1.00	38.81
ATOM	942	CB	ARG	A	96	173.386	35.432	13.159	1.00	38.58
ATOM	943	CG	ARG	A	96	174.757	35.415	13.848	1.00	36.99
ATOM	944	CD	ARG	A	96	175.919	35.584	12.869	1.00	35.28
ATOM	945	NE	ARG	A	96	177.207	35.640	13.562	1.00	37.59
ATOM	947	CZ	ARG	A	96	177.887	34.582	14.004	1.00	38.32
ATOM	948	NH1	ARG	A	96	177.425	33.351	13.832	1.00	41.87
ATOM	951	NH2	ARG	A	96	179.024	34.758	14.658	1.00	34.85
ATOM	954	C	ARG	A	96	171.909	35.972	15.183	1.00	38.25
ATOM	955	O	ARG	A	96	171.091	35.672	16.048	1.00	38.45
ATOM	956	N	PHE	A	97	172.506	37.161	15.158	1.00	36.05
ATOM	958	CA	PHE	A	97	172.236	38.157	16.189	1.00	32.76
ATOM	959	CB	PHE	A	97	173.521	38.856	16.634	1.00	29.39
ATOM	960	CG	PHE	A	97	174.503	37.958	17.311	1.00	27.30
ATOM	961	CD1	PHE	A	97	174.214	37.392	18.538	1.00	26.91
ATOM	962	CD2	PHE	A	97	175.733	37.695	16.728	1.00	29.62
ATOM	963	CE1	PHE	A	97	175.140	36.578	19.175	1.00	28.35
ATOM	964	CE2	PHE	A	97	176.661	36.886	17.358	1.00	27.60
ATOM	965	CZ	PHE	A	97	176.364	36.327	18.582	1.00	28.30
ATOM	966	C	PHE	A	97	171.261	39.208	15.693	1.00	34.25

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ATOM	967	O	PHE A	97	171.016	40.199	16.387	1.00	33.16
ATOM	968	N	LEU A	98	170.739	39.012	14.484	1.00	36.60
ATOM	970	CA	LEU A	98	169.790	39.952	13.888	1.00	39.31
ATOM	971	CB	LEU A	98	169.874	39.905	12.361	1.00	38.74
ATOM	972	CG	LEU A	98	169.875	41.238	11.608	1.00	38.17
ATOM	973	CD1	LEU A	98	169.883	40.951	10.128	1.00	40.67
ATOM	974	CD2	LEU A	98	168.680	42.093	11.971	1.00	38.92
ATOM	975	C	LEU A	98	168.366	39.631	14.317	1.00	40.51
ATOM	976	O	LEU A	98	167.854	38.554	14.016	1.00	42.93
ATOM	977	N	LYS A	99	167.737	40.570	15.018	1.00	41.98
ATOM	979	CA	LYS A	99	166.365	40.410	15.488	1.00	42.37
ATOM	980	CB	LYS A	99	166.258	40.705	16.989	1.00	41.90
ATOM	981	CG	LYS A	99	166.690	39.566	17.898	1.00	45.06
ATOM	982	CD	LYS A	99	166.389	39.882	19.361	1.00	47.68
ATOM	983	CE	LYS A	99	166.638	38.671	20.250	1.00	51.09
ATOM	984	NZ	LYS A	99	166.251	38.895	21.674	1.00	53.87
ATOM	988	C	LYS A	99	165.440	41.351	14.727	1.00	43.86
ATOM	989	O	LYS A	99	165.634	42.573	14.739	1.00	45.41
ATOM	990	N	MET A	100	164.438	40.785	14.064	1.00	43.74
ATOM	992	CA	MET A	100	163.479	41.575	13.310	1.00	43.78
ATOM	993	CB	MET A	100	163.576	41.234	11.826	1.00	44.48
ATOM	994	CG	MET A	100	164.885	41.651	11.195	1.00	45.32
ATOM	995	SD	MET A	100	165.190	40.802	9.654	1.00	49.68
ATOM	996	CE	MET A	100	165.736	39.168	10.290	1.00	44.16
ATOM	997	C	MET A	100	162.078	41.292	13.832	1.00	44.78
ATOM	998	O	MET A	100	161.693	40.132	13.987	1.00	44.97
ATOM	999	N	SER A	101	161.335	42.352	14.140	1.00	46.57
ATOM	1001	CA	SER A	101	159.971	42.221	14.650	1.00	47.86
ATOM	1002	CB	SER A	101	159.934	42.469	16.162	1.00	49.20
ATOM	1003	OG	SER A	101	160.560	43.693	16.509	1.00	51.70
ATOM	1005	C	SER A	101	159.009	43.168	13.937	1.00	48.68
ATOM	1006	O	SER A	101	159.428	44.161	13.332	1.00	48.84
ATOM	1007	N	GLY A	102	157.722	42.839	13.986	1.00	49.46

SUBSTITUTE SHEET (RULE 26)

ATOM	1009	CA	GLY	A	102	156.716	43.664	13.343	1.00 49.50
ATOM	1010	C	GLY	A	102	155.359	42.989	13.341	1.00 48.98
ATOM	1011	O	GLY	A	102	155.251	41.795	13.613	1.00 50.09
ATOM	1012	N	ASN	A	103	154.317	43.766	13.079	1.00 48.68
ATOM	1014	CA	ASN	A	103	152.957	43.243	13.042	1.00 47.35
ATOM	1015	CB	ASN	A	103	151.945	44.349	13.391	1.00 49.87
ATOM	1016	CG	ASN	A	103	152.061	44.837	14.840	1.00 51.69
ATOM	1017	OD1	ASN	A	103	153.067	45.423	15.234	1.00 53.03
ATOM	1018	ND2	ASN	A	103	151.014	44.621	15.625	1.00 53.17
ATOM	1021	C	ASN	A	103	152.703	42.743	11.625	1.00 46.11
ATOM	1022	O	ASN	A	103	153.459	43.073	10.708	1.00 45.99
ATOM	1023	N	PHE	A	104	151.667	41.926	11.451	1.00 44.40
ATOM	1025	CA	PHE	A	104	151.306	41.410	10.131	1.00 42.85
ATOM	1026	CB	PHE	A	104	151.987	40.051	9.835	1.00 42.59
ATOM	1027	CG	PHE	A	104	151.319	38.849	10.482	1.00 41.53
ATOM	1028	CD1	PHE	A	104	151.650	38.458	11.776	1.00 39.25
ATOM	1029	CD2	PHE	A	104	150.380	38.095	9.778	1.00 39.79
ATOM	1030	CE1	PHE	A	104	151.058	37.339	12.357	1.00 37.60
ATOM	1031	CE2	PHE	A	104	149.784	36.976	10.353	1.00 36.72
ATOM	1032	CZ	PHE	A	104	150.125	36.599	11.644	1.00 37.02
ATOM	1033	C	PHE	A	104	149.788	41.303	10.006	1.00 42.22
ATOM	1034	O	PHE	A	104	149.081	41.251	11.014	1.00 43.09
ATOM	1035	N	ASP	A	105	149.298	41.346	8.771	1.00 41.99
ATOM	1037	CA	ASP	A	105	147.874	41.227	8.475	1.00 41.67
ATOM	1038	CB	ASP	A	105	147.352	42.455	7.724	1.00 43.33
ATOM	1039	CG	ASP	A	105	146.986	43.602	8.648	1.00 46.56
ATOM	1040	OD1	ASP	A	105	146.898	43.395	9.876	1.00 49.37
ATOM	1041	OD2	ASP	A	105	146.770	44.720	8.141	1.00 51.38
ATOM	1042	C	ASP	A	105	147.658	39.985	7.622	1.00 41.95
ATOM	1043	O	ASP	A	105	148.470	39.655	6.758	1.00 42.85
ATOM	1044	N	LEU	A	106	146.538	39.322	7.841	1.00 40.99
ATOM	1046	CA	LEU	A	106	146.220	38.115	7.115	1.00 39.85
ATOM	1047	CB	LEU	A	106	146.424	36.934	8.058	1.00 38.87
ATOM	1048	CG	LEU	A	106	146.224	35.489	7.629	1.00 39.36

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ATOM	1049	CD1	LEU	A	106	146.825	34.605	8.690	1.00 40.16
ATOM	1050	CD2	LEU	A	106	144.758	35.175	7.464	1.00 41.07
ATOM	1051	C	LEU	A	106	144.767	38.248	6.698	1.00 40.07
ATOM	1052	O	LEU	A	106	143.968	38.841	7.414	1.00 41.85
ATOM	1053	N	SER	A	107	144.427	37.748	5.523	1.00 41.19
ATOM	1055	CA	SER	A	107	143.054	37.830	5.061	1.00 43.48
ATOM	1056	CB	SER	A	107	142.911	38.907	3.979	1.00 45.09
ATOM	1057	OG	SER	A	107	143.440	40.155	4.402	1.00 50.35
ATOM	1059	C	SER	A	107	142.633	36.484	4.502	1.00 43.83
ATOM	1060	O	SER	A	107	143.290	35.957	3.610	1.00 44.06
ATOM	1061	N	ILE	A	108	141.587	35.900	5.077	1.00 45.70
ATOM	1063	CA	ILE	A	108	141.056	34.617	4.615	1.00 47.58
ATOM	1064	CB	ILE	A	108	140.829	33.644	5.789	1.00 46.97
ATOM	1065	CG2	ILE	A	108	140.174	32.368	5.296	1.00 46.17
ATOM	1066	CG1	ILE	A	108	142.157	33.327	6.474	1.00 47.60
ATOM	1067	CD1	ILE	A	108	142.042	32.368	7.637	1.00 49.72
ATOM	1068	C	ILE	A	108	139.716	34.922	3.959	1.00 48.97
ATOM	1069	O	ILE	A	108	138.818	35.433	4.619	1.00 51.76
ATOM	1070	N	GLU	A	109	139.582	34.652	2.664	1.00 50.18
ATOM	1072	CA	GLU	A	109	138.328	34.938	1.968	1.00 52.80
ATOM	1073	CB	GLU	A	109	138.506	36.067	0.956	1.00 58.29
ATOM	1074	CG	GLU	A	109	138.871	37.409	1.556	1.00 67.61
ATOM	1075	CD	GLU	A	109	138.896	38.510	0.518	1.00 72.52
ATOM	1076	OE1	GLU	A	109	139.591	38.345	-0.510	1.00 76.73
ATOM	1077	OE2	GLU	A	109	138.212	39.536	0.725	1.00 74.66
ATOM	1078	C	GLU	A	109	137.771	33.733	1.244	1.00 51.51
ATOM	1079	O	GLU	A	109	138.449	32.717	1.091	1.00 51.13
ATOM	1080	N	GLY	A	110	136.539	33.867	0.767	1.00 50.94
ATOM	1082	CA	GLY	A	110	135.904	32.778	0.051	1.00 49.27
ATOM	1083	C	GLY	A	110	135.714	31.551	0.920	1.00 48.08
ATOM	1084	O	GLY	A	110	135.972	30.419	0.488	1.00 47.03
ATOM	1085	N	MET	A	111	135.318	31.784	2.168	1.00 46.98
ATOM	1087	CA	MET	A	111	135.078	30.699	3.104	1.00 44.78

SUBSTITUTE SHEET (RULE 26)

ATOM	1088	CB	MET	A	111	135.376	31.143	4.536	1.00 44.81
ATOM	1089	CG	MET	A	111	135.062	30.092	5.570	1.00 44.07
ATOM	1090	SD	MET	A	111	135.669	30.518	7.178	1.00 49.80
ATOM	1091	CE	MET	A	111	136.833	29.192	7.434	1.00 46.06
ATOM	1092	C	MET	A	111	133.630	30.242	2.970	1.00 42.64
ATOM	1093	O	MET	A	111	132.712	31.061	2.960	1.00 40.20
ATOM	1094	N	SER	A	112	133.446	28.935	2.846	1.00 41.52
ATOM	1096	CA	SER	A	112	132.133	28.334	2.708	1.00 41.82
ATOM	1097	CB	SER	A	112	132.045	27.607	1.360	1.00 43.85
ATOM	1098	OG	SER	A	112	130.997	26.648	1.321	1.00 49.86
ATOM	1100	C	SER	A	112	131.908	27.363	3.861	1.00 41.93
ATOM	1101	O	SER	A	112	132.725	26.467	4.097	1.00 41.84
ATOM	1102	N	ILE	A	113	130.816	27.569	4.592	1.00 42.07
ATOM	1104	CA	ILE	A	113	130.444	26.722	5.725	1.00 40.13
ATOM	1105	CB	ILE	A	113	130.310	27.546	7.027	1.00 39.38
ATOM	1106	CG2	ILE	A	113	130.227	26.620	8.231	1.00 39.63
ATOM	1107	CG1	ILE	A	113	131.505	28.480	7.190	1.00 35.78
ATOM	1108	CD1	ILE	A	113	131.284	29.547	8.225	1.00 38.78
ATOM	1109	C	ILE	A	113	129.083	26.105	5.405	1.00 40.48
ATOM	1110	O	ILE	A	113	128.118	26.821	5.117	1.00 40.10
ATOM	1111	N	SER	A	114	129.016	24.780	5.414	1.00 40.69
ATOM	1113	CA	SER	A	114	127.775	24.076	5.126	1.00 39.86
ATOM	1114	CB	SER	A	114	127.915	23.277	3.835	1.00 39.27
ATOM	1115	OG	SER	A	114	126.695	22.645	3.486	1.00 45.23
ATOM	1117	C	SER	A	114	127.489	23.152	6.297	1.00 40.43
ATOM	1118	O	SER	A	114	128.370	22.407	6.730	1.00 42.01
ATOM	1119	N	ALA	A	115	126.261	23.198	6.804	1.00 40.94
ATOM	1121	CA	ALA	A	115	125.863	22.380	7.947	1.00 40.28
ATOM	1122	CB	ALA	A	115	125.990	23.186	9.227	1.00 41.97
ATOM	1123	C	ALA	A	115	124.446	21.856	7.814	1.00 39.55
ATOM	1124	O	ALA	A	115	123.551	22.581	7.385	1.00 38.65
ATOM	1125	N	ASP	A	116	124.248	20.603	8.213	1.00 39.92
ATOM	1127	CA	ASP	A	116	122.943	19.954	8.155	1.00 40.51
ATOM	1128	CB	ASP	A	116	123.092	18.513	7.672	1.00 44.07

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ATOM	1129	CG	ASP	A	116	123.359	18.421	6.184	1.00 48.91
ATOM	1130	OD1	ASP	A	116	124.455	18.829	5.741	1.00 53.18
ATOM	1131	OD2	ASP	A	116	122.467	17.940	5.455	1.00 52.27
ATOM	1132	C	ASP	A	116	122.241	19.956	9.504	1.00 39.36
ATOM	1133	O	ASP	A	116	122.804	19.501	10.495	1.00 40.86
ATOM	1134	N	LEU	A	117	121.009	20.459	9.537	1.00 38.66
ATOM	1136	CA	LEU	A	117	120.220	20.508	10.766	1.00 35.83
ATOM	1137	CB	LEU	A	117	119.578	21.888	10.944	1.00 34.68
ATOM	1138	CG	LEU	A	117	120.493	23.096	11.140	1.00 34.59
ATOM	1139	CD1	LEU	A	117	119.667	24.361	11.279	1.00 35.67
ATOM	1140	CD2	LEU	A	117	121.346	22.895	12.370	1.00 35.88
ATOM	1141	C	LEU	A	117	119.131	19.437	10.721	1.00 35.13
ATOM	1142	O	LEU	A	117	118.287	19.435	9.824	1.00 35.15
ATOM	1143	N	LYS	A	118	119.155	18.531	11.691	1.00 35.41
ATOM	1145	CA	LYS	A	118	118.180	17.450	11.776	1.00 34.03
ATOM	1146	CB	LYS	A	118	118.896	16.128	12.047	1.00 36.61
ATOM	1147	CG	LYS	A	118	118.027	14.904	11.907	1.00 41.84
ATOM	1148	CD	LYS	A	118	118.870	13.640	11.890	1.00 45.83
ATOM	1149	CE	LYS	A	118	117.998	12.400	11.773	1.00 49.70
ATOM	1150	NZ	LYS	A	118	117.098	12.434	10.576	1.00 52.85
ATOM	1154	C	LYS	A	118	117.184	17.760	12.884	1.00 32.08
ATOM	1155	O	LYS	A	118	117.572	18.045	14.014	1.00 30.72
ATOM	1156	N	LEU	A	119	115.900	17.737	12.545	1.00 34.05
ATOM	1158	CA	LEU	A	119	114.838	18.036	13.503	1.00 33.03
ATOM	1159	CB	LEU	A	119	113.782	18.917	12.844	1.00 30.64
ATOM	1160	CG	LEU	A	119	114.277	20.278	12.372	1.00 26.32
ATOM	1161	CD1	LEU	A	119	113.434	20.751	11.229	1.00 27.43
ATOM	1162	CD2	LEU	A	119	114.230	21.258	13.511	1.00 29.44
ATOM	1163	C	LEU	A	119	114.192	16.771	14.065	1.00 33.62
ATOM	1164	O	LEU	A	119	113.904	15.819	13.334	1.00 32.69
ATOM	1165	N	GLY	A	120	113.952	16.776	15.368	1.00 33.78
ATOM	1167	CA	GLY	A	120	113.353	15.624	16.000	1.00 33.21
ATOM	1168	C	GLY	A	120	112.431	16.059	17.109	1.00 34.60

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ATOM	1169	O	GLY	A	120	112.238	17.250	17.340	1.00 34.75
ATOM	1170	N	SER	A	121	111.883	15.086	17.817	1.00 37.06
ATOM	1172	CA	SER	A	121	110.961	15.355	18.902	1.00 40.83
ATOM	1173	CB	SER	A	121	109.541	14.982	18.464	1.00 41.68
ATOM	1174	OG	SER	A	121	108.638	14.924	19.554	1.00 44.95
ATOM	1176	C	SER	A	121	111.357	14.527	20.108	1.00 43.32
ATOM	1177	O	SER	A	121	111.990	13.476	19.975	1.00 44.77
ATOM	1178	N	ASN	A	122	111.034	15.038	21.287	1.00 45.49
ATOM	1180	CA	ASN	A	122	111.308	14.330	22.525	1.00 48.51
ATOM	1181	CB	ASN	A	122	112.014	15.244	23.523	1.00 47.83
ATOM	1182	CG	ASN	A	122	112.693	14.474	24.633	1.00 49.31
ATOM	1183	OD1	ASN	A	122	112.445	13.283	24.827	1.00 48.55
ATOM	1184	ND2	ASN	A	122	113.574	15.146	25.359	1.00 52.06
ATOM	1187	C	ASN	A	122	109.925	13.955	23.040	1.00 50.18
ATOM	1188	O	ASN	A	122	109.197	14.810	23.534	1.00 51.08
ATOM	1189	N	PRO	A	123	109.530	12.678	22.895	1.00 51.66
ATOM	1190	CD	PRO	A	123	110.378	11.593	22.375	1.00 51.97
ATOM	1191	CA	PRO	A	123	108.229	12.152	23.323	1.00 51.81
ATOM	1192	CB	PRO	A	123	108.291	10.696	22.875	1.00 52.33
ATOM	1193	CG	PRO	A	123	109.744	10.377	22.996	1.00 52.53
ATOM	1194	C	PRO	A	123	107.903	12.255	24.808	1.00 52.83
ATOM	1195	O	PRO	A	123	106.777	12.593	25.171	1.00 54.24
ATOM	1196	N	THR	A	124	108.879	11.969	25.664	1.00 53.70
ATOM	1198	CA	THR	A	124	108.658	12.016	27.109	1.00 55.10
ATOM	1199	CB	THR	A	124	109.782	11.285	27.873	1.00 55.63
ATOM	1200	OG1	THR	A	124	111.038	11.556	27.244	1.00 57.26
ATOM	1202	CG2	THR	A	124	109.536	9.782	27.879	1.00 57.40
ATOM	1203	C	THR	A	124	108.467	13.418	27.687	1.00 54.39
ATOM	1204	O	THR	A	124	108.031	13.568	28.833	1.00 56.00
ATOM	1205	N	SER	A	125	108.794	14.439	26.901	1.00 52.41
ATOM	1207	CA	SER	A	125	108.647	15.824	27.345	1.00 49.57
ATOM	1208	CB	SER	A	125	110.023	16.448	27.598	1.00 49.34
ATOM	1209	OG	SER	A	125	110.859	16.328	26.459	1.00 50.88
ATOM	1211	C	SER	A	125	107.855	16.676	26.355	1.00 46.68

SUBSTITUTE SHEET (RULE 26)

ATOM	1212	O	SER	A	125	107.366	17.747	26.702	1.00 46.69
ATOM	1213	N	GLY	A	126	107.734	16.191	25.123	1.00 44.84
ATOM	1215	CA	GLY	A	126	107.008	16.906	24.091	1.00 42.00
ATOM	1216	C	GLY	A	126	107.739	18.113	23.537	1.00 40.90
ATOM	1217	O	GLY	A	126	107.125	18.953	22.885	1.00 41.68
ATOM	1218	N	LYS	A	127	109.044	18.201	23.780	1.00 40.27
ATOM	1220	CA	LYS	A	127	109.846	19.330	23.303	1.00 38.06
ATOM	1221	CB	LYS	A	127	110.914	19.708	24.340	1.00 41.48
ATOM	1222	CG	LYS	A	127	110.408	20.194	25.705	1.00 44.59
ATOM	1223	CD	LYS	A	127	109.966	21.657	25.697	1.00 48.40
ATOM	1224	CE	LYS	A	127	109.668	22.142	27.118	1.00 49.68
ATOM	1225	NZ	LYS	A	127	109.045	23.498	27.151	1.00 50.76
ATOM	1229	C	LYS	A	127	110.533	18.984	21.980	1.00 36.38
ATOM	1230	O	LYS	A	127	110.916	17.827	21.751	1.00 36.93
ATOM	1231	N	PRO	A	128	110.705	19.980	21.093	1.00 33.49
ATOM	1232	CD	PRO	A	128	110.310	21.395	21.226	1.00 31.99
ATOM	1233	CA	PRO	A	128	111.354	19.747	19.803	1.00 31.41
ATOM	1234	CB	PRO	A	128	111.023	21.020	19.037	1.00 31.27
ATOM	1235	CG	PRO	A	128	111.085	22.056	20.109	1.00 29.23
ATOM	1236	C	PRO	A	128	112.853	19.611	20.007	1.00 31.58
ATOM	1237	O	PRO	A	128	113.389	20.080	21.010	1.00 31.45
ATOM	1238	N	THR	A	129	113.523	18.936	19.087	1.00 31.21
ATOM	1240	CA	THR	A	129	114.960	18.779	19.181	1.00 30.79
ATOM	1241	CB	THR	A	129	115.377	17.332	19.510	1.00 29.38
ATOM	1242	OG1	THR	A	129	114.952	16.451	18.467	1.00 30.58
ATOM	1244	CG2	THR	A	129	114.773	16.886	20.818	1.00 27.50
ATOM	1245	C	THR	A	129	115.568	19.185	17.856	1.00 32.76
ATOM	1246	O	THR	A	129	114.907	19.148	16.813	1.00 32.88
ATOM	1247	N	ILE	A	130	116.828	19.582	17.904	1.00 35.82
ATOM	1249	CA	ILE	A	130	117.554	19.999	16.717	1.00 37.64
ATOM	1250	CB	ILE	A	130	117.302	21.506	16.401	1.00 38.78
ATOM	1251	CG2	ILE	A	130	117.277	22.335	17.665	1.00 40.02
ATOM	1252	CG1	ILE	A	130	118.345	22.042	15.425	1.00 38.94

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ATOM	1253	CD1	ILE	A	130	118.138	21.591	14.014	1.00 42.34
ATOM	1254	C	ILE	A	130	119.026	19.740	16.985	1.00 38.69
ATOM	1255	O	ILE	A	130	119.534	20.085	18.048	1.00 40.22
ATOM	1256	N	THR	A	131	119.681	19.039	16.069	1.00 39.62
ATOM	1258	CA	THR	A	131	121.098	18.748	16.217	1.00 40.39
ATOM	1259	CB	THR	A	131	121.351	17.318	16.747	1.00 40.39
ATOM	1260	OG1	THR	A	131	120.833	16.354	15.825	1.00 40.07
ATOM	1262	CG2	THR	A	131	120.696	17.124	18.113	1.00 43.21
ATOM	1263	C	THR	A	131	121.788	18.927	14.878	1.00 41.17
ATOM	1264	O	THR	A	131	121.139	18.951	13.839	1.00 41.86
ATOM	1265	N	CYS	A	132	123.099	19.107	14.911	1.00 42.72
ATOM	1267	CA	CYS	A	132	123.875	19.284	13.696	1.00 42.81
ATOM	1268	CB	CYS	A	132	124.963	20.326	13.932	1.00 42.56
ATOM	1269	SG	CYS	A	132	126.009	20.629	12.530	1.00 38.05
ATOM	1270	C	CYS	A	132	124.494	17.940	13.333	1.00 44.48
ATOM	1271	O	CYS	A	132	125.370	17.446	14.041	1.00 46.08
ATOM	1272	N	SER	A	133	124.019	17.344	12.244	1.00 45.05
ATOM	1274	CA	SER	A	133	124.508	16.045	11.794	1.00 45.93
ATOM	1275	CB	SER	A	133	123.410	15.315	11.015	1.00 47.62
ATOM	1276	OG	SER	A	133	122.962	16.082	9.908	1.00 51.90
ATOM	1278	C	SER	A	133	125.793	16.072	10.966	1.00 45.39
ATOM	1279	O	SER	A	133	126.512	15.078	10.916	1.00 46.00
ATOM	1280	N	SER	A	134	126.056	17.182	10.282	1.00 45.72
ATOM	1282	CA	SER	A	134	127.257	17.322	9.453	1.00 45.69
ATOM	1283	CB	SER	A	134	127.048	16.672	8.073	1.00 47.17
ATOM	1284	OG	SER	A	134	127.221	15.263	8.110	1.00 50.20
ATOM	1286	C	SER	A	134	127.642	18.788	9.265	1.00 44.02
ATOM	1287	O	SER	A	134	126.775	19.663	9.212	1.00 45.04
ATOM	1288	N	CYS	A	135	128.939	19.047	9.145	1.00 42.35
ATOM	1290	CA	CYS	A	135	129.442	20.398	8.941	1.00 40.67
ATOM	1291	C	CYS	A	135	130.728	20.345	8.144	1.00 41.67
ATOM	1292	O	CYS	A	135	131.469	19.361	8.216	1.00 40.71
ATOM	1293	CB	CYS	A	135	129.718	21.084	10.274	1.00 39.61
ATOM	1294	SG	CYS	A	135	130.296	22.800	10.094	1.00 34.66

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ATOM	1295	N	SER	A	136	130.975	21.383	7.354	1.00 43.65
ATOM	1297	CA	SER	A	136	132.192	21.451	6.562	1.00 45.71
ATOM	1298	CB	SER	A	136	132.131	20.504	5.357	1.00 48.55
ATOM	1299	OG	SER	A	136	131.231	20.961	4.363	1.00 54.17
ATOM	1301	C	SER	A	136	132.465	22.874	6.114	1.00 45.23
ATOM	1302	O	SER	A	136	131.582	23.551	5.583	1.00 44.66
ATOM	1303	N	SER	A	137	133.673	23.339	6.411	1.00 45.29
ATOM	1305	CA	SER	A	137	134.110	24.671	6.040	1.00 45.90
ATOM	1306	CB	SER	A	137	134.896	25.302	7.186	1.00 45.32
ATOM	1307	OG	SER	A	137	135.302	26.620	6.867	1.00 46.54
ATOM	1309	C	SER	A	137	134.990	24.514	4.806	1.00 47.49
ATOM	1310	O	SER	A	137	135.330	23.392	4.416	1.00 48.14
ATOM	1311	N	HIS	A	138	135.371	25.630	4.200	1.00 48.87
ATOM	1313	CA	HIS	A	138	136.196	25.599	3.003	1.00 49.64
ATOM	1314	CB	HIS	A	138	135.338	25.149	1.811	1.00 53.41
ATOM	1315	CG	HIS	A	138	136.097	24.992	0.529	1.00 56.80
ATOM	1316	CD2	HIS	A	138	136.712	23.915	-0.016	1.00 58.14
ATOM	1317	ND1	HIS	A	138	136.268	26.025	-0.368	1.00 59.15
ATOM	1319	CE1	HIS	A	138	136.956	25.592	-1.412	1.00 59.11
ATOM	1320	NE2	HIS	A	138	137.238	24.316	-1.222	1.00 59.30
ATOM	1322	C	HIS	A	138	136.779	26.983	2.742	1.00 49.79
ATOM	1323	O	HIS	A	138	136.042	27.938	2.510	1.00 49.66
ATOM	1324	N	ILE	A	139	138.102	27.082	2.808	1.00 50.32
ATOM	1326	CA	ILE	A	139	138.822	28.330	2.565	1.00 50.43
ATOM	1327	CB	ILE	A	139	139.937	28.519	3.606	1.00 50.04
ATOM	1328	CG2	ILE	A	139	140.876	29.651	3.195	1.00 46.81
ATOM	1329	CG1	ILE	A	139	139.313	28.751	4.982	1.00 49.41
ATOM	1330	CD1	ILE	A	139	140.310	28.816	6.105	1.00 53.48
ATOM	1331	C	ILE	A	139	139.430	28.312	1.159	1.00 51.98
ATOM	1332	O	ILE	A	139	140.019	27.311	0.743	1.00 51.75
ATOM	1333	N	ASN	A	140	139.267	29.409	0.425	1.00 53.16
ATOM	1335	CA	ASN	A	140	139.792	29.503	-0.935	1.00 54.65
ATOM	1336	CB	ASN	A	140	138.824	30.291	-1.832	1.00 57.65

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ATOM	1337	CG	ASN	A	140	139.311	30.400	-3.276	1.00 60.64
ATOM	1338	OD1	ASN	A	140	139.295	31.483	-3.867	1.00 61.18
ATOM	1339	ND2	ASN	A	140	139.742	29.279	-3.848	1.00 62.27
ATOM	1342	C	ASN	A	140	141.203	30.092	-1.024	1.00 53.67
ATOM	1343	O	ASN	A	140	142.097	29.463	-1.589	1.00 53.36
ATOM	1344	N	SER	A	141	141.401	31.289	-0.474	1.00 52.97
ATOM	1346	CA	SER	A	141	142.711	31.943	-0.518	1.00 52.86
ATOM	1347	CB	SER	A	141	142.728	33.051	-1.585	1.00 52.81
ATOM	1348	OG	SER	A	141	141.928	34.167	-1.218	1.00 50.44
ATOM	1350	C	SER	A	141	143.114	32.526	0.832	1.00 52.49
ATOM	1351	O	SER	A	141	142.263	32.778	1.684	1.00 54.02
ATOM	1352	N	VAL	A	142	144.415	32.724	1.023	1.00 52.25
ATOM	1354	CA	VAL	A	142	144.947	33.290	2.256	1.00 50.52
ATOM	1355	CB	VAL	A	142	145.583	32.203	3.152	1.00 49.93
ATOM	1356	CG1	VAL	A	142	146.214	32.826	4.380	1.00 49.68
ATOM	1357	CG2	VAL	A	142	144.533	31.197	3.577	1.00 50.61
ATOM	1358	C	VAL	A	142	145.990	34.335	1.880	1.00 51.54
ATOM	1359	O	VAL	A	142	147.083	34.000	1.418	1.00 50.89
ATOM	1360	N	HIS	A	143	145.611	35.603	2.021	1.00 54.44
ATOM	1362	CA	HIS	A	143	146.470	36.742	1.709	1.00 57.63
ATOM	1363	CB	HIS	A	143	145.639	37.904	1.154	1.00 60.05
ATOM	1364	CG	HIS	A	143	145.323	37.789	-0.306	1.00 65.61
ATOM	1365	CD2	HIS	A	143	145.600	38.615	-1.343	1.00 67.19
ATOM	1366	ND1	HIS	A	143	144.632	36.722	-0.841	1.00 67.65
ATOM	1368	CE1	HIS	A	143	144.498	36.896	-2.145	1.00 68.08
ATOM	1369	NE2	HIS	A	143	145.078	38.037	-2.473	1.00 67.35
ATOM	1371	C	HIS	A	143	147.229	37.232	2.936	1.00 58.93
ATOM	1372	O	HIS	A	143	146.663	37.914	3.791	1.00 58.93
ATOM	1373	N	VAL	A	144	148.510	36.893	3.012	1.00 60.40
ATOM	1375	CA	VAL	A	144	149.347	37.316	4.124	1.00 62.35
ATOM	1376	CB	VAL	A	144	150.423	36.270	4.441	1.00 61.34
ATOM	1377	CG1	VAL	A	144	151.245	36.703	5.641	1.00 62.08
ATOM	1378	CG2	VAL	A	144	149.771	34.938	4.709	1.00 62.01
ATOM	1379	C	VAL	A	144	150.000	38.632	3.724	1.00 64.53

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ATOM	1380	O	VAL	A	144	150.971	38.658	2.971	1.00 64.35
ATOM	1381	N	HIS	A	145	149.440	39.729	4.214	1.00 67.48
ATOM	1383	CA	HIS	A	145	149.945	41.050	3.886	1.00 71.08
ATOM	1384	CB	HIS	A	145	148.791	42.045	3.771	1.00 72.13
ATOM	1385	CG	HIS	A	145	147.860	41.751	2.642	1.00 74.06
ATOM	1386	CD2	HIS	A	145	148.098	41.536	1.327	1.00 74.26
ATOM	1387	ND1	HIS	A	145	146.497	41.640	2.810	1.00 75.07
ATOM	1389	CE1	HIS	A	145	145.934	41.370	1.646	1.00 75.64
ATOM	1390	NE2	HIS	A	145	146.884	41.303	0.730	1.00 75.46
ATOM	1392	C	HIS	A	145	150.998	41.600	4.830	1.00 73.50
ATOM	1393	O	HIS	A	145	150.742	42.560	5.553	1.00 74.03
ATOM	1394	N	ILE	A	146	152.184	40.999	4.826	1.00 76.22
ATOM	1396	CA	ILE	A	146	153.277	41.497	5.660	1.00 78.65
ATOM	1397	CB	ILE	A	146	154.282	40.374	6.055	1.00 77.20
ATOM	1398	CG2	ILE	A	146	155.320	40.905	7.037	1.00 75.80
ATOM	1399	CG1	ILE	A	146	153.545	39.214	6.729	1.00 76.58
ATOM	1400	CD1	ILE	A	146	154.451	38.091	7.184	1.00 75.69
ATOM	1401	C	ILE	A	146	153.972	42.574	4.815	1.00 81.85
ATOM	1402	O	ILE	A	146	155.107	42.970	5.082	1.00 81.33
ATOM	1403	N	SER	A	147	153.273	43.023	3.774	1.00 85.84
ATOM	1405	CA	SER	A	147	153.758	44.049	2.864	1.00 89.73
ATOM	1406	CB	SER	A	147	152.736	44.267	1.737	1.00 89.11
ATOM	1407	OG	SER	A	147	152.396	43.046	1.097	1.00 89.21
ATOM	1409	C	SER	A	147	153.983	45.354	3.637	1.00 92.25
ATOM	1410	O	SER	A	147	153.080	46.188	3.753	1.00 94.01
ATOM	1411	N	ALA	A	148	155.182	45.494	4.197	1.00 92.99
ATOM	1413	CA	ALA	A	148	155.568	46.675	4.967	1.00 92.04
ATOM	1414	CB	ALA	A	148	155.027	46.577	6.395	1.00 92.57
ATOM	1415	C	ALA	A	148	157.092	46.778	4.982	1.00 91.03
ATOM	1416	O	ALA	A	148	157.657	47.869	5.086	1.00 92.24
ATOM	1417	N	ALA	A	149	157.749	45.628	4.875	1.00 88.25
ATOM	1419	CA	ALA	A	149	159.201	45.558	4.864	1.00 85.00
ATOM	1420	CB	ALA	A	149	159.720	45.237	6.263	1.00 85.37

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ATOM	1421	C	ALA	A	149	159.624	44.474	3.874	1.00 82.20
ATOM	1422	O	ALA	A	149	158.888	43.508	3.650	1.00 83.34
ATOM	1423	N	SER	A	150	160.785	44.657	3.252	1.00 77.07
ATOM	1425	CA	SER	A	150	161.304	43.690	2.293	1.00 71.37
ATOM	1426	CB	SER	A	150	162.463	44.313	1.509	1.00 72.17
ATOM	1427	OG	SER	A	150	162.092	45.574	0.968	1.00 72.35
ATOM	1429	C	SER	A	150	161.768	42.434	3.037	1.00 66.95
ATOM	1430	O	SER	A	150	162.927	42.330	3.440	1.00 66.96
ATOM	1431	N	VAL	A	151	160.847	41.496	3.240	1.00 60.88
ATOM	1433	CA	VAL	A	151	161.146	40.257	3.949	1.00 54.82
ATOM	1434	CB	VAL	A	151	160.736	40.381	5.446	1.00 55.79
ATOM	1435	CG1	VAL	A	151	159.233	40.593	5.584	1.00 55.13
ATOM	1436	CG2	VAL	A	151	161.206	39.176	6.242	1.00 55.16
ATOM	1437	C	VAL	A	151	160.417	39.104	3.259	1.00 51.49
ATOM	1438	O	VAL	A	151	159.721	38.308	3.887	1.00 51.42
ATOM	1439	N	GLY	A	152	160.639	38.992	1.957	1.00 48.87
ATOM	1441	CA	GLY	A	152	159.994	37.961	1.167	1.00 45.39
ATOM	1442	C	GLY	A	152	160.100	36.531	1.656	1.00 42.87
ATOM	1443	O	GLY	A	152	159.144	35.766	1.543	1.00 43.01
ATOM	1444	N	TRP	A	153	161.245	36.160	2.211	1.00 41.58
ATOM	1446	CA	TRP	A	153	161.432	34.795	2.682	1.00 41.92
ATOM	1447	CB	TRP	A	153	162.853	34.591	3.196	1.00 42.78
ATOM	1448	CG	TRP	A	153	163.153	35.267	4.501	1.00 43.10
ATOM	1449	CD2	TRP	A	153	163.738	36.559	4.678	1.00 43.00
ATOM	1450	CE2	TRP	A	153	163.953	36.738	6.064	1.00 43.32
ATOM	1451	CE3	TRP	A	153	164.112	37.583	3.796	1.00 45.47
ATOM	1452	CD1	TRP	A	153	163.022	34.730	5.760	1.00 42.27
ATOM	1453	NE1	TRP	A	153	163.508	35.607	6.700	1.00 42.43
ATOM	1455	CZ2	TRP	A	153	164.528	37.897	6.587	1.00 44.70
ATOM	1456	CZ3	TRP	A	153	164.686	38.738	4.317	1.00 47.45
ATOM	1457	CH2	TRP	A	153	164.889	38.885	5.701	1.00 47.30
ATOM	1458	C	TRP	A	153	160.442	34.393	3.763	1.00 41.11
ATOM	1459	O	TRP	A	153	160.053	33.236	3.852	1.00 41.06
ATOM	1460	N	LEU	A	154	160.045	35.357	4.585	1.00 40.39

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ATOM	1462	CA	LEU	A	154	159.109	35.103	5.669	1.00 38.88
ATOM	1463	CB	LEU	A	154	159.080	36.284	6.618	1.00 37.14
ATOM	1464	CG	LEU	A	154	158.607	35.931	8.011	1.00 35.27
ATOM	1465	CD1	LEU	A	154	159.491	34.860	8.602	1.00 35.45
ATOM	1466	CD2	LEU	A	154	158.655	37.166	8.838	1.00 37.10
ATOM	1467	C	LEU	A	154	157.721	34.847	5.115	1.00 38.87
ATOM	1468	O	LEU	A	154	156.997	33.985	5.611	1.00 39.93
ATOM	1469	N	ILE	A	155	157.357	35.596	4.079	1.00 40.01
ATOM	1471	CA	ILE	A	155	156.062	35.435	3.430	1.00 40.45
ATOM	1472	CB	ILE	A	155	155.765	36.579	2.454	1.00 39.45
ATOM	1473	CG2	ILE	A	155	154.467	36.307	1.721	1.00 39.70
ATOM	1474	CG1	ILE	A	155	155.679	37.906	3.215	1.00 39.53
ATOM	1475	CD1	ILE	A	155	155.426	39.114	2.337	1.00 39.05
ATOM	1476	C	ILE	A	155	156.048	34.106	2.686	1.00 42.61
ATOM	1477	O	ILE	A	155	155.015	33.435	2.619	1.00 44.53
ATOM	1478	N	GLN	A	156	157.187	33.745	2.100	1.00 43.49
ATOM	1480	CA	GLN	A	156	157.323	32.475	1.398	1.00 44.17
ATOM	1481	CB	GLN	A	156	158.708	32.368	0.760	1.00 48.67
ATOM	1482	CG	GLN	A	156	159.097	30.954	0.310	1.00 55.67
ATOM	1483	CD	GLN	A	156	160.369	30.440	0.988	1.00 59.91
ATOM	1484	OE1	GLN	A	156	160.673	30.802	2.125	1.00 61.96
ATOM	1485	NE2	GLN	A	156	161.114	29.593	0.285	1.00 60.94
ATOM	1488	C	GLN	A	156	157.163	31.384	2.452	1.00 43.64
ATOM	1489	O	GLN	A	156	156.445	30.408	2.249	1.00 43.84
ATOM	1490	N	LEU	A	157	157.834	31.581	3.585	1.00 43.44
ATOM	1492	CA	LEU	A	157	157.794	30.653	4.704	1.00 41.27
ATOM	1493	CB	LEU	A	157	158.644	31.175	5.866	1.00 42.44
ATOM	1494	CG	LEU	A	157	160.152	30.930	5.797	1.00 42.39
ATOM	1495	CD1	LEU	A	157	160.873	31.722	6.876	1.00 41.73
ATOM	1496	CD2	LEU	A	157	160.426	29.447	5.948	1.00 42.15
ATOM	1497	C	LEU	A	157	156.372	30.423	5.173	1.00 40.27
ATOM	1498	O	LEU	A	157	155.948	29.280	5.328	1.00 41.05
ATOM	1499	N	PHE	A	158	155.620	31.497	5.378	1.00 39.18

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ATOM	1501	CA	PHE	A	158	154.246	31.341	5.821	1.00 41.38
ATOM	1502	CB	PHE	A	158	153.519	32.684	5.927	1.00 40.94
ATOM	1503	CG	PHE	A	158	152.145	32.570	6.537	1.00 43.98
ATOM	1504	CD1	PHE	A	158	151.068	32.087	5.788	1.00 44.07
ATOM	1505	CD2	PHE	A	158	151.939	32.886	7.878	1.00 43.45
ATOM	1506	CE1	PHE	A	158	149.814	31.915	6.367	1.00 42.96
ATOM	1507	CE2	PHE	A	158	150.690	32.718	8.465	1.00 41.63
ATOM	1508	CZ	PHE	A	158	149.626	32.231	7.707	1.00 43.20
ATOM	1509	C	PHE	A	158	153.472	30.409	4.893	1.00 42.96
ATOM	1510	O	PHE	A	158	152.862	29.443	5.350	1.00 44.53
ATOM	1511	N	HIS	A	159	153.513	30.682	3.594	1.00 45.12
ATOM	1513	CA	HIS	A	159	152.790	29.860	2.624	1.00 46.02
ATOM	1514	CB	HIS	A	159	152.808	30.507	1.230	1.00 45.21
ATOM	1515	CG	HIS	A	159	152.049	31.796	1.145	1.00 44.03
ATOM	1516	CD2	HIS	A	159	152.477	33.081	1.099	1.00 44.13
ATOM	1517	ND1	HIS	A	159	150.674	31.851	1.087	1.00 44.17
ATOM	1519	CE1	HIS	A	159	150.285	33.111	1.012	1.00 45.07
ATOM	1520	NE2	HIS	A	159	151.360	33.878	1.016	1.00 45.02
ATOM	1522	C	HIS	A	159	153.314	28.426	2.524	1.00 47.97
ATOM	1523	O	HIS	A	159	152.530	27.491	2.353	1.00 48.86
ATOM	1524	N	LYS	A	160	154.624	28.253	2.678	1.00 49.77
ATOM	1526	CA	LYS	A	160	155.246	26.935	2.562	1.00 50.79
ATOM	1527	CB	LYS	A	160	156.664	27.080	1.990	1.00 51.90
ATOM	1528	CG	LYS	A	160	157.285	25.768	1.539	1.00 53.77
ATOM	1529	CD	LYS	A	160	158.669	25.957	0.950	1.00 54.99
ATOM	1530	CE	LYS	A	160	159.130	24.690	0.231	1.00 57.16
ATOM	1531	NZ	LYS	A	160	158.253	24.330	-0.934	1.00 55.19
ATOM	1535	C	LYS	A	160	155.286	26.065	3.825	1.00 51.12
ATOM	1536	O	LYS	A	160	155.537	24.862	3.736	1.00 52.93
ATOM	1537	N	LYS	A	161	155.031	26.646	4.991	1.00 49.90
ATOM	1539	CA	LYS	A	161	155.086	25.873	6.229	1.00 48.78
ATOM	1540	CB	LYS	A	161	156.340	26.263	7.016	1.00 51.36
ATOM	1541	CG	LYS	A	161	157.660	25.983	6.310	1.00 55.24
ATOM	1542	CD	LYS	A	161	158.186	24.592	6.626	1.00 59.40

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ATOM	1543	CE	LYS	A	161	158.484	24.443	8.114	1.00 61.04
ATOM	1544	NZ	LYS	A	161	159.015	23.095	8.464	1.00 62.60
ATOM	1548	C	LYS	A	161	153.875	26.012	7.149	1.00 47.20
ATOM	1549	O	LYS	A	161	153.460	25.042	7.787	1.00 46.35
ATOM	1550	N	ILE	A	162	153.311	27.214	7.209	1.00 46.07
ATOM	1552	CA	ILE	A	162	152.186	27.506	8.094	1.00 45.42
ATOM	1553	CB	ILE	A	162	152.421	28.854	8.806	1.00 45.05
ATOM	1554	CG2	ILE	A	162	151.211	29.251	9.646	1.00 45.73
ATOM	1555	CG1	ILE	A	162	153.679	28.764	9.670	1.00 43.35
ATOM	1556	CD1	ILE	A	162	154.015	30.042	10.353	1.00 43.37
ATOM	1557	C	ILE	A	162	150.764	27.483	7.520	1.00 45.58
ATOM	1558	O	ILE	A	162	149.849	26.960	8.157	1.00 45.52
ATOM	1559	N	GLU	A	163	150.570	28.036	6.329	1.00 46.35
ATOM	1561	CA	GLU	A	163	149.239	28.093	5.731	1.00 47.82
ATOM	1562	CB	GLU	A	163	149.310	28.624	4.302	1.00 49.25
ATOM	1563	CG	GLU	A	163	147.956	29.028	3.735	1.00 51.68
ATOM	1564	CD	GLU	A	163	147.965	29.204	2.224	1.00 52.54
ATOM	1565	OE1	GLU	A	163	149.007	29.597	1.658	1.00 53.57
ATOM	1566	OE2	GLU	A	163	146.918	28.941	1.599	1.00 53.52
ATOM	1567	C	GLU	A	163	148.470	26.775	5.746	1.00 47.94
ATOM	1568	O	GLU	A	163	147.289	26.757	6.069	1.00 49.00
ATOM	1569	N	SER	A	164	149.142	25.678	5.420	1.00 49.09
ATOM	1571	CA	SER	A	164	148.510	24.360	5.383	1.00 49.75
ATOM	1572	CB	SER	A	164	149.486	23.327	4.818	1.00 50.94
ATOM	1573	OG	SER	A	164	149.971	23.737	3.548	1.00 56.63
ATOM	1575	C	SER	A	164	147.953	23.865	6.717	1.00 49.89
ATOM	1576	O	SER	A	164	147.100	22.982	6.739	1.00 52.82
ATOM	1577	N	ALA	A	165	148.442	24.415	7.824	1.00 48.05
ATOM	1579	CA	ALA	A	165	147.978	24.017	9.151	1.00 44.58
ATOM	1580	CB	ALA	A	165	149.153	23.920	10.109	1.00 45.11
ATOM	1581	C	ALA	A	165	146.947	25.009	9.678	1.00 43.87
ATOM	1582	O	ALA	A	165	145.980	24.626	10.335	1.00 43.62
ATOM	1583	N	LEU	A	166	147.169	26.287	9.391	1.00 43.88

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ATOM	1585	CA	LEU	A	166	146.267	27.349	9.812	1.00 44.57
ATOM	1586	CB	LEU	A	166	146.783	28.701	9.313	1.00 41.17
ATOM	1587	CG	LEU	A	166	145.977	29.957	9.655	1.00 39.43
ATOM	1588	CD1	LEU	A	166	146.438	30.508	10.979	1.00 40.32
ATOM	1589	CD2	LEU	A	166	146.165	31.005	8.577	1.00 39.33
ATOM	1590	C	LEU	A	166	144.870	27.094	9.246	1.00 47.80
ATOM	1591	O	LEU	A	166	143.899	27.003	9.995	1.00 50.31
ATOM	1592	N	ARG	A	167	144.777	26.946	7.927	1.00 49.83
ATOM	1594	CA	ARG	A	167	143.493	26.714	7.274	1.00 53.68
ATOM	1595	CB	ARG	A	167	143.659	26.564	5.753	1.00 54.31
ATOM	1596	CG	ARG	A	167	144.488	25.354	5.329	1.00 57.76
ATOM	1597	CD	ARG	A	167	144.282	24.966	3.869	1.00 58.03
ATOM	1598	NE	ARG	A	167	144.657	26.032	2.948	1.00 56.39
ATOM	1600	CZ	ARG	A	167	143.786	26.753	2.256	1.00 55.99
ATOM	1601	NH1	ARG	A	167	142.485	26.525	2.380	1.00 56.36
ATOM	1604	NH2	ARG	A	167	144.214	27.699	1.436	1.00 55.25
ATOM	1607	C	ARG	A	167	142.774	25.495	7.836	1.00 56.26
ATOM	1608	O	ARG	A	167	141.570	25.544	8.088	1.00 58.47
ATOM	1609	N	ASN	A	168	143.517	24.418	8.077	1.00 59.06
ATOM	1611	CA	ASN	A	168	142.924	23.188	8.596	1.00 60.42
ATOM	1612	CB	ASN	A	168	143.936	22.037	8.586	1.00 63.69
ATOM	1613	CG	ASN	A	168	143.264	20.670	8.594	1.00 69.44
ATOM	1614	OD1	ASN	A	168	142.186	20.491	8.021	1.00 73.41
ATOM	1615	ND2	ASN	A	168	143.902	19.696	9.232	1.00 71.02
ATOM	1618	C	ASN	A	168	142.358	23.378	9.995	1.00 58.54
ATOM	1619	O	ASN	A	168	141.291	22.857	10.312	1.00 59.34
ATOM	1620	N	LYS	A	169	143.059	24.138	10.826	1.00 56.61
ATOM	1622	CA	LYS	A	169	142.591	24.380	12.179	1.00 54.57
ATOM	1623	CB	LYS	A	169	143.732	24.882	13.065	1.00 56.85
ATOM	1624	CG	LYS	A	169	143.365	25.002	14.540	1.00 60.65
ATOM	1625	CD	LYS	A	169	144.599	24.927	15.425	1.00 65.37
ATOM	1626	CE	LYS	A	169	145.276	23.560	15.329	1.00 68.82
ATOM	1627	NZ	LYS	A	169	146.576	23.504	16.062	1.00 70.63
ATOM	1631	C	LYS	A	169	141.439	25.372	12.173	1.00 51.59

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ATOM	1632	O	LYS	A	169	140.570	25.327	13.035	1.00 51.73
ATOM	1633	N	MET	A	170	141.426	26.264	11.192	1.00 49.16
ATOM	1635	CA	MET	A	170	140.362	27.251	11.090	1.00 47.96
ATOM	1636	CB	MET	A	170	140.733	28.340	10.087	1.00 49.44
ATOM	1637	CG	MET	A	170	139.792	29.528	10.105	1.00 52.89
ATOM	1638	SD	MET	A	170	139.730	30.289	11.734	1.00 55.23
ATOM	1639	CE	MET	A	170	141.170	31.310	11.695	1.00 55.26
ATOM	1640	C	MET	A	170	139.075	26.565	10.659	1.00 45.37
ATOM	1641	O	MET	A	170	137.989	26.892	11.139	1.00 46.51
ATOM	1642	N	ASN	A	171	139.207	25.601	9.759	1.00 42.65
ATOM	1644	CA	ASN	A	171	138.063	24.858	9.268	1.00 41.99
ATOM	1645	CB	ASN	A	171	138.448	24.034	8.039	1.00 42.92
ATOM	1646	CG	ASN	A	171	138.644	24.889	6.795	1.00 43.47
ATOM	1647	OD1	ASN	A	171	138.041	25.957	6.658	1.00 44.24
ATOM	1648	ND2	ASN	A	171	139.478	24.415	5.875	1.00 44.77
ATOM	1651	C	ASN	A	171	137.487	23.962	10.353	1.00 42.70
ATOM	1652	O	ASN	A	171	136.284	23.701	10.374	1.00 43.68
ATOM	1653	N	SER	A	172	138.341	23.502	11.263	1.00 44.20
ATOM	1655	CA	SER	A	172	137.898	22.645	12.358	1.00 45.11
ATOM	1656	CB	SER	A	172	139.069	21.841	12.935	1.00 46.36
ATOM	1657	OG	SER	A	172	140.094	22.685	13.438	1.00 49.96
ATOM	1659	C	SER	A	172	137.230	23.474	13.454	1.00 44.96
ATOM	1660	O	SER	A	172	136.204	23.069	14.005	1.00 47.71
ATOM	1661	N	GLN	A	173	137.811	24.635	13.759	1.00 43.91
ATOM	1663	CA	GLN	A	173	137.276	25.541	14.776	1.00 40.36
ATOM	1664	CB	GLN	A	173	138.214	26.730	14.990	1.00 41.61
ATOM	1665	CG	GLN	A	173	139.444	26.421	15.816	1.00 43.62
ATOM	1666	CD	GLN	A	173	139.095	25.943	17.205	1.00 46.78
ATOM	1667	OE1	GLN	A	173	138.657	26.722	18.052	1.00 50.29
ATOM	1668	NE2	GLN	A	173	139.279	24.654	17.448	1.00 48.32
ATOM	1671	C	GLN	A	173	135.893	26.047	14.386	1.00 38.81
ATOM	1672	O	GLN	A	173	134.990	26.098	15.218	1.00 38.42
ATOM	1673	N	VAL	A	174	135.734	26.423	13.120	1.00 36.59

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ATOM	1675	CA	VAL	A	174	134.456	26.912	12.621	1.00 34.47
ATOM	1676	CB	VAL	A	174	134.559	27.328	11.147	1.00 32.46
ATOM	1677	CG1	VAL	A	174	133.183	27.559	10.564	1.00 32.42
ATOM	1678	CG2	VAL	A	174	135.380	28.601	11.037	1.00 31.13
ATOM	1679	C	VAL	A	174	133.363	25.861	12.810	1.00 34.32
ATOM	1680	O	VAL	A	174	132.350	26.130	13.445	1.00 36.14
ATOM	1681	N	CYS	A	175	133.586	24.652	12.308	1.00 35.02
ATOM	1683	CA	CYS	A	175	132.601	23.591	12.460	1.00 35.40
ATOM	1684	C	CYS	A	175	132.440	23.152	13.906	1.00 36.62
ATOM	1685	O	CYS	A	175	131.405	22.597	14.284	1.00 37.92
ATOM	1686	CB	CYS	A	175	132.925	22.396	11.573	1.00 33.94
ATOM	1687	SG	CYS	A	175	132.302	22.595	9.876	1.00 42.37
ATOM	1688	N	GLU	A	176	133.459	23.386	14.720	1.00 38.42
ATOM	1690	CA	GLU	A	176	133.365	23.034	16.123	1.00 40.14
ATOM	1691	CB	GLU	A	176	134.739	23.093	16.793	1.00 43.35
ATOM	1692	CG	GLU	A	176	134.747	22.502	18.193	1.00 50.93
ATOM	1693	CD	GLU	A	176	136.132	22.385	18.783	1.00 53.93
ATOM	1694	OE1	GLU	A	176	136.867	21.459	18.382	1.00 58.04
ATOM	1695	OE2	GLU	A	176	136.481	23.207	19.658	1.00 57.02
ATOM	1696	C	GLU	A	176	132.386	24.024	16.772	1.00 40.43
ATOM	1697	O	GLU	A	176	131.498	23.627	17.528	1.00 41.95
ATOM	1698	N	LYS	A	177	132.507	25.301	16.419	1.00 39.36
ATOM	1700	CA	LYS	A	177	131.625	26.332	16.956	1.00 38.66
ATOM	1701	CB	LYS	A	177	132.074	27.729	16.510	1.00 38.94
ATOM	1702	CG	LYS	A	177	133.403	28.194	17.089	1.00 40.75
ATOM	1703	CD	LYS	A	177	133.336	28.424	18.592	1.00 40.88
ATOM	1704	CE	LYS	A	177	134.694	28.852	19.152	1.00 40.13
ATOM	1705	NZ	LYS	A	177	134.688	28.995	20.637	1.00 40.04
ATOM	1709	C	LYS	A	177	130.190	26.099	16.503	1.00 37.24
ATOM	1710	O	LYS	A	177	129.277	26.078	17.318	1.00 39.39
ATOM	1711	N	VAL	A	178	130.002	25.901	15.204	1.00 35.46
ATOM	1713	CA	VAL	A	178	128.676	25.676	14.641	1.00 33.61
ATOM	1714	CB	VAL	A	178	128.747	25.442	13.124	1.00 31.21
ATOM	1715	CG1	VAL	A	178	127.365	25.166	12.568	1.00 32.70

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ATOM	1716	CG2	VAL	A	178	129.346	26.652	12.446	1.00 31.16
ATOM	1717	C	VAL	A	178	127.960	24.505	15.299	1.00 34.02
ATOM	1718	O	VAL	A	178	126.844	24.656	15.784	1.00 36.09
ATOM	1719	N	THR	A	179	128.611	23.349	15.338	1.00 34.04
ATOM	1721	CA	THR	A	179	128.018	22.167	15.947	1.00 35.60
ATOM	1722	CB	THR	A	179	128.977	20.968	15.865	1.00 32.77
ATOM	1723	OG1	THR	A	179	129.372	20.775	14.505	1.00 32.73
ATOM	1725	CG2	THR	A	179	128.296	19.706	16.330	1.00 35.18
ATOM	1726	C	THR	A	179	127.634	22.428	17.408	1.00 39.92
ATOM	1727	O	THR	A	179	126.554	22.037	17.858	1.00 42.33
ATOM	1728	N	ASN	A	180	128.497	23.131	18.132	1.00 43.69
ATOM	1730	CA	ASN	A	180	128.244	23.435	19.537	1.00 44.92
ATOM	1731	CB	ASN	A	180	129.496	23.991	20.213	1.00 49.20
ATOM	1732	CG	ASN	A	180	130.522	22.920	20.532	1.00 53.34
ATOM	1733	OD1	ASN	A	180	131.550	23.213	21.140	1.00 58.92
ATOM	1734	ND2	ASN	A	180	130.258	21.680	20.126	1.00 53.15
ATOM	1737	C	ASN	A	180	127.101	24.406	19.738	1.00 44.35
ATOM	1738	O	ASN	A	180	126.252	24.194	20.593	1.00 46.90
ATOM	1739	N	SER	A	181	127.095	25.487	18.972	1.00 42.77
ATOM	1741	CA	SER	A	181	126.047	26.481	19.084	1.00 42.55
ATOM	1742	CB	SER	A	181	126.274	27.605	18.076	1.00 46.25
ATOM	1743	OG	SER	A	181	127.508	28.261	18.319	1.00 51.45
ATOM	1745	C	SER	A	181	124.686	25.841	18.869	1.00 41.46
ATOM	1746	O	SER	A	181	123.720	26.203	19.528	1.00 43.31
ATOM	1747	N	VAL	A	182	124.610	24.870	17.969	1.00 41.03
ATOM	1749	CA	VAL	A	182	123.346	24.195	17.712	1.00 40.50
ATOM	1750	CB	VAL	A	182	123.468	23.177	16.565	1.00 40.39
ATOM	1751	CG1	VAL	A	182	122.133	22.489	16.333	1.00 41.54
ATOM	1752	CG2	VAL	A	182	123.918	23.874	15.295	1.00 39.67
ATOM	1753	C	VAL	A	182	122.865	23.481	18.970	1.00 41.04
ATOM	1754	O	VAL	A	182	121.831	23.836	19.536	1.00 41.32
ATOM	1755	N	SER	A	183	123.647	22.510	19.429	1.00 42.02
ATOM	1757	CA	SER	A	183	123.311	21.735	20.616	1.00 41.82

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ATOM	1758	CB	SER	A	183	124.339	20.620	20.828	1.00 42.01
ATOM	1759	OG	SER	A	183	124.180	19.588	19.867	1.00 47.44
ATOM	1761	C	SER	A	183	123.187	22.553	21.895	1.00 41.66
ATOM	1762	O	SER	A	183	122.251	22.358	22.673	1.00 43.45
ATOM	1763	N	SER	A	184	124.120	23.472	22.102	1.00 40.24
ATOM	1765	CA	SER	A	184	124.143	24.293	23.305	1.00 40.26
ATOM	1766	CB	SER	A	184	125.590	24.639	23.670	1.00 42.61
ATOM	1767	OG	SER	A	184	126.340	23.468	23.947	1.00 47.85
ATOM	1769	C	SER	A	184	123.307	25.567	23.312	1.00 39.22
ATOM	1770	O	SER	A	184	122.991	26.088	24.382	1.00 40.56
ATOM	1771	N	GLU	A	185	122.942	26.078	22.145	1.00 37.87
ATOM	1773	CA	GLU	A	185	122.169	27.313	22.098	1.00 37.71
ATOM	1774	CB	GLU	A	185	123.060	28.485	21.683	1.00 40.53
ATOM	1775	CG	GLU	A	185	124.010	28.960	22.768	1.00 45.79
ATOM	1776	CD	GLU	A	185	124.987	30.024	22.296	1.00 50.89
ATOM	1777	OE1	GLU	A	185	124.887	30.490	21.138	1.00 55.20
ATOM	1778	OE2	GLU	A	185	125.872	30.390	23.097	1.00 55.19
ATOM	1779	C	GLU	A	185	120.934	27.277	21.225	1.00 35.83
ATOM	1780	O	GLU	A	185	119.921	27.861	21.584	1.00 38.77
ATOM	1781	N	LEU	A	186	121.008	26.605	20.082	1.00 34.44
ATOM	1783	CA	LEU	A	186	119.864	26.533	19.187	1.00 33.39
ATOM	1784	CB	LEU	A	186	120.269	25.978	17.818	1.00 30.92
ATOM	1785	CG	LEU	A	186	119.709	26.645	16.553	1.00 26.02
ATOM	1786	CD1	LEU	A	186	119.228	25.581	15.601	1.00 23.97
ATOM	1787	CD2	LEU	A	186	118.581	27.619	16.867	1.00 25.38
ATOM	1788	C	LEU	A	186	118.794	25.652	19.802	1.00 34.20
ATOM	1789	O	LEU	A	186	117.655	26.083	19.963	1.00 35.35
ATOM	1790	N	GLN	A	187	119.168	24.433	20.181	1.00 35.06
ATOM	1792	CA	GLN	A	187	118.218	23.500	20.778	1.00 37.32
ATOM	1793	CB	GLN	A	187	118.856	22.130	21.031	1.00 38.08
ATOM	1794	CG	GLN	A	187	117.859	21.104	21.549	1.00 39.72
ATOM	1795	CD	GLN	A	187	118.388	19.696	21.506	1.00 39.64
ATOM	1796	OE1	GLN	A	187	118.203	18.984	20.520	1.00 42.24
ATOM	1797	NE2	GLN	A	187	119.031	19.272	22.585	1.00 43.70

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ATOM	1800	C	GLN	A	187	117.548	24.041	22.041	1.00 36.63
ATOM	1801	O	GLN	A	187	116.325	24.022	22.138	1.00 40.27
ATOM	1802	N	PRO	A	188	118.333	24.493	23.038	1.00 36.32
ATOM	1803	CD	PRO	A	188	119.782	24.293	23.223	1.00 38.65
ATOM	1804	CA	PRO	A	188	117.748	25.033	24.268	1.00 35.72
ATOM	1805	CB	PRO	A	188	118.977	25.432	25.075	1.00 34.46
ATOM	1806	CG	PRO	A	188	119.933	24.364	24.730	1.00 35.29
ATOM	1807	C	PRO	A	188	116.829	26.231	24.030	1.00 36.20
ATOM	1808	O	PRO	A	188	115.933	26.490	24.835	1.00 38.62
ATOM	1809	N	TYR	A	189	117.062	26.983	22.957	1.00 35.08
ATOM	1811	CA	TYR	A	189	116.203	28.122	22.667	1.00 33.10
ATOM	1812	CB	TYR	A	189	116.799	29.059	21.625	1.00 30.49
ATOM	1813	CG	TYR	A	189	115.767	30.037	21.113	1.00 29.52
ATOM	1814	CD1	TYR	A	189	115.222	30.996	21.958	1.00 28.37
ATOM	1815	CE1	TYR	A	189	114.211	31.842	21.523	1.00 27.60
ATOM	1816	CD2	TYR	A	189	115.274	29.950	19.808	1.00 28.40
ATOM	1817	CE2	TYR	A	189	114.261	30.792	19.366	1.00 26.35
ATOM	1818	CZ	TYR	A	189	113.737	31.732	20.231	1.00 25.96
ATOM	1819	OH	TYR	A	189	112.735	32.568	19.815	1.00 27.51
ATOM	1821	C	TYR	A	189	114.841	27.660	22.186	1.00 34.73
ATOM	1822	O	TYR	A	189	113.824	28.113	22.694	1.00 38.35
ATOM	1823	N	PHE	A	190	114.811	26.771	21.197	1.00 36.21
ATOM	1825	CA	PHE	A	190	113.538	26.288	20.684	1.00 37.47
ATOM	1826	CB	PHE	A	190	113.697	25.649	19.302	1.00 38.76
ATOM	1827	CG	PHE	A	190	113.522	26.633	18.177	1.00 41.54
ATOM	1828	CD1	PHE	A	190	112.273	27.194	17.920	1.00 40.00
ATOM	1829	CD2	PHE	A	190	114.610	27.042	17.406	1.00 43.58
ATOM	1830	CE1	PHE	A	190	112.109	28.146	16.919	1.00 39.03
ATOM	1831	CE2	PHE	A	190	114.454	27.999	16.398	1.00 40.39
ATOM	1832	CZ	PHE	A	190	113.201	28.550	16.159	1.00 39.28
ATOM	1833	C	PHE	A	190	112.768	25.408	21.662	1.00 37.92
ATOM	1834	O	PHE	A	190	111.655	24.960	21.380	1.00 38.40
ATOM	1835	N	GLN	A	191	113.351	25.193	22.835	1.00 36.94

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ATOM	1837	CA	GLN	A	191	112.685	24.425	23.869	1.00 36.24
ATOM	1838	CB	GLN	A	191	113.637	23.426	24.529	1.00 36.06
ATOM	1839	CG	GLN	A	191	113.987	22.259	23.609	1.00 37.66
ATOM	1840	CD	GLN	A	191	114.786	21.170	24.287	1.00 36.77
ATOM	1841	OE1	GLN	A	191	115.365	21.379	25.349	1.00 38.68
ATOM	1842	NE2	GLN	A	191	114.828	19.997	23.669	1.00 35.78
ATOM	1845	C	GLN	A	191	112.042	25.369	24.881	1.00 37.61
ATOM	1846	O	GLN	A	191	111.621	24.945	25.956	1.00 38.67
ATOM	1847	N	THR	A	192	111.992	26.659	24.541	1.00 38.44
ATOM	1849	CA	THR	A	192	111.338	27.650	25.392	1.00 37.16
ATOM	1850	CB	THR	A	192	111.946	29.055	25.263	1.00 36.82
ATOM	1851	OG1	THR	A	192	111.937	29.461	23.890	1.00 37.79
ATOM	1853	CG2	THR	A	192	113.357	29.083	25.802	1.00 36.99
ATOM	1854	C	THR	A	192	109.894	27.702	24.913	1.00 37.14
ATOM	1855	O	THR	A	192	109.082	28.485	25.403	1.00 38.53
ATOM	1856	N	LEU	A	193	109.604	26.884	23.906	1.00 38.31
ATOM	1858	CA	LEU	A	193	108.273	26.765	23.339	1.00 40.73
ATOM	1859	CB	LEU	A	193	108.325	25.772	22.174	1.00 42.93
ATOM	1860	CG	LEU	A	193	107.191	25.727	21.151	1.00 44.96
ATOM	1861	CD1	LEU	A	193	107.000	27.100	20.518	1.00 45.48
ATOM	1862	CD2	LEU	A	193	107.531	24.696	20.085	1.00 44.59
ATOM	1863	C	LEU	A	193	107.403	26.218	24.472	1.00 40.91
ATOM	1864	O	LEU	A	193	107.788	25.265	25.150	1.00 41.30
ATOM	1865	N	PRO	A	194	106.230	26.824	24.707	1.00 41.79
ATOM	1866	CD	PRO	A	194	105.632	27.950	23.974	1.00 41.39
ATOM	1867	CA	PRO	A	194	105.334	26.373	25.777	1.00 41.80
ATOM	1868	CB	PRO	A	194	104.217	27.420	25.754	1.00 42.00
ATOM	1869	CG	PRO	A	194	104.823	28.603	25.045	1.00 42.94
ATOM	1870	C	PRO	A	194	104.755	24.985	25.522	1.00 41.75
ATOM	1871	O	PRO	A	194	104.174	24.734	24.469	1.00 44.72
ATOM	1872	N	VAL	A	195	104.930	24.080	26.476	1.00 39.33
ATOM	1874	CA	VAL	A	195	104.383	22.738	26.338	1.00 37.64
ATOM	1875	CB	VAL	A	195	105.403	21.659	26.756	1.00 37.05
ATOM	1876	CG1	VAL	A	195	104.744	20.295	26.840	1.00 34.56

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ATOM	1877	CG2	VAL	A	195	106.515	21.607	25.747	1.00 36.43
ATOM	1878	C	VAL	A	195	103.118	22.644	27.183	1.00 38.20
ATOM	1879	O	VAL	A	195	102.062	22.245	26.694	1.00 40.04
ATOM	1880	N	MET	A	196	103.234	23.007	28.454	1.00 38.05
ATOM	1882	CA	MET	A	196	102.103	22.987	29.370	1.00 37.71
ATOM	1883	CB	MET	A	196	102.414	22.128	30.592	1.00 40.52
ATOM	1884	CG	MET	A	196	102.756	20.681	30.283	1.00 43.85
ATOM	1885	SD	MET	A	196	101.356	19.738	29.695	1.00 42.31
ATOM	1886	CE	MET	A	196	100.644	19.226	31.232	1.00 41.10
ATOM	1887	C	MET	A	196	101.924	24.428	29.796	1.00 37.52
ATOM	1888	O	MET	A	196	102.521	24.877	30.771	1.00 40.72
ATOM	1889	N	THR	A	197	101.134	25.167	29.039	1.00 36.00
ATOM	1891	CA	THR	A	197	100.914	26.565	29.335	1.00 34.89
ATOM	1892	CB	THR	A	197	100.650	27.324	28.036	1.00 37.85
ATOM	1893	OG1	THR	A	197	101.329	26.660	26.963	1.00 41.31
ATOM	1895	CG2	THR	A	197	101.177	28.733	28.131	1.00 39.84
ATOM	1896	C	THR	A	197	99.751	26.772	30.302	1.00 32.85
ATOM	1897	O	THR	A	197	98.594	26.571	29.939	1.00 33.57
ATOM	1898	N	LYS	A	198	100.061	27.122	31.545	1.00 29.63
ATOM	1900	CA	LYS	A	198	99.036	27.372	32.551	1.00 27.13
ATOM	1901	CB	LYS	A	198	99.630	27.266	33.952	1.00 26.01
ATOM	1902	CG	LYS	A	198	98.609	27.379	35.047	1.00 26.97
ATOM	1903	CD	LYS	A	198	99.269	27.457	36.389	1.00 31.48
ATOM	1904	CE	LYS	A	198	98.232	27.489	37.482	1.00 33.31
ATOM	1905	NZ	LYS	A	198	97.393	26.263	37.448	1.00 38.94
ATOM	1909	C	LYS	A	198	98.555	28.789	32.307	1.00 26.60
ATOM	1910	O	LYS	A	198	99.365	29.706	32.264	1.00 27.53
ATOM	1911	N	ILE	A	199	97.248	28.975	32.154	1.00 26.62
ATOM	1913	CA	ILE	A	199	96.711	30.298	31.878	1.00 23.94
ATOM	1914	CB	ILE	A	199	95.817	30.283	30.613	1.00 25.54
ATOM	1915	CG2	ILE	A	199	96.561	29.614	29.477	1.00 26.32
ATOM	1916	CG1	ILE	A	199	94.543	29.487	30.843	1.00 23.67
ATOM	1917	CD1	ILE	A	199	93.795	29.189	29.564	1.00 22.95

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ATOM	1918	C	ILE A 199	95.992	30.954	33.041	1.00	25.86
ATOM	1919	O	ILE A 199	95.827	32.169	33.061	1.00	28.61
ATOM	1920	N	ASP A 200	95.561	30.148	34.007	1.00	27.99
ATOM	1922	CA	ASP A 200	94.878	30.651	35.197	1.00	26.92
ATOM	1923	CB	ASP A 200	93.484	31.220	34.867	1.00	26.06
ATOM	1924	CG	ASP A 200	92.582	30.234	34.151	1.00	24.60
ATOM	1925	OD1	ASP A 200	92.621	29.037	34.465	1.00	26.68
ATOM	1926	OD2	ASP A 200	91.813	30.664	33.271	1.00	28.99
ATOM	1927	C	ASP A 200	94.805	29.589	36.289	1.00	27.44
ATOM	1928	O	ASP A 200	95.509	28.591	36.225	1.00	29.73
ATOM	1929	N	SER A 201	93.966	29.808	37.294	1.00	28.30
ATOM	1931	CA	SER A 201	93.825	28.859	38.397	1.00	30.40
ATOM	1932	CB	SER A 201	93.032	29.507	39.531	1.00	31.85
ATOM	1933	OG	SER A 201	91.882	30.170	39.026	1.00	39.39
ATOM	1935	C	SER A 201	93.137	27.562	38.000	1.00	29.79
ATOM	1936	O	SER A 201	93.230	26.557	38.695	1.00	31.67
ATOM	1937	N	VAL A 202	92.430	27.604	36.884	1.00	30.29
ATOM	1939	CA	VAL A 202	91.683	26.457	36.409	1.00	29.89
ATOM	1940	CB	VAL A 202	90.284	26.911	35.932	1.00	28.59
ATOM	1941	CG1	VAL A 202	89.426	25.723	35.568	1.00	30.45
ATOM	1942	CG2	VAL A 202	89.613	27.740	36.998	1.00	28.22
ATOM	1943	C	VAL A 202	92.346	25.667	35.282	1.00	31.71
ATOM	1944	O	VAL A 202	92.752	24.520	35.470	1.00	33.93
ATOM	1945	N	ALA A 203	92.463	26.291	34.115	1.00	31.10
ATOM	1947	CA	ALA A 203	92.997	25.621	32.944	1.00	29.58
ATOM	1948	CB	ALA A 203	92.039	25.821	31.767	1.00	29.01
ATOM	1949	C	ALA A 203	94.416	25.908	32.497	1.00	28.91
ATOM	1950	O	ALA A 203	95.096	26.807	33.001	1.00	27.86
ATOM	1951	N	GLY A 204	94.822	25.124	31.503	1.00	26.23
ATOM	1953	CA	GLY A 204	96.124	25.227	30.894	1.00	22.94
ATOM	1954	C	GLY A 204	95.936	24.686	29.495	1.00	22.27
ATOM	1955	O	GLY A 204	94.900	24.098	29.206	1.00	24.27
ATOM	1956	N	ILE A 205	96.909	24.893	28.619	1.00	22.81
ATOM	1958	CA	ILE A 205	96.817	24.402	27.250	1.00	21.62

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ATOM	1959	CB	ILE	A	205	96.868	25.542	26.222	1.00 17.56
ATOM	1960	CG2	ILE	A	205	96.458	25.020	24.870	1.00 17.14
ATOM	1961	CG1	ILE	A	205	95.928	26.672	26.627	1.00 16.69
ATOM	1962	CD1	ILE	A	205	96.021	27.878	25.753	1.00 10.87
ATOM	1963	C	ILE	A	205	98.010	23.492	27.008	1.00 24.34
ATOM	1964	O	ILE	A	205	99.120	23.784	27.452	1.00 26.93
ATOM	1965	N	ASN	A	206	97.770	22.374	26.333	1.00 24.44
ATOM	1967	CA	ASN	A	206	98.817	21.414	26.039	1.00 20.90
ATOM	1968	CB	ASN	A	206	98.280	19.989	26.217	1.00 21.75
ATOM	1969	CG	ASN	A	206	99.359	18.921	26.099	1.00 22.44
ATOM	1970	OD1	ASN	A	206	99.077	17.727	26.218	1.00 26.27
ATOM	1971	ND2	ASN	A	206	100.593	19.337	25.878	1.00 24.68
ATOM	1974	C	ASN	A	206	99.285	21.629	24.614	1.00 22.48
ATOM	1975	O	ASN	A	206	98.579	21.296	23.664	1.00 23.50
ATOM	1976	N	TYR	A	207	100.458	22.239	24.475	1.00 23.09
ATOM	1978	CA	TYR	A	207	101.065	22.517	23.179	1.00 21.41
ATOM	1979	CB	TYR	A	207	101.647	23.927	23.165	1.00 17.69
ATOM	1980	CG	TYR	A	207	100.625	25.008	22.986	1.00 16.56
ATOM	1981	CD1	TYR	A	207	99.703	24.943	21.961	1.00 19.32
ATOM	1982	CE1	TYR	A	207	98.795	25.963	21.757	1.00 20.24
ATOM	1983	CD2	TYR	A	207	100.611	26.122	23.810	1.00 18.10
ATOM	1984	CE2	TYR	A	207	99.711	27.144	23.613	1.00 18.49
ATOM	1985	CZ	TYR	A	207	98.809	27.060	22.581	1.00 18.16
ATOM	1986	OH	TYR	A	207	97.939	28.089	22.332	1.00 21.72
ATOM	1988	C	TYR	A	207	102.181	21.532	22.868	1.00 24.14
ATOM	1989	O	TYR	A	207	103.111	21.851	22.134	1.00 25.16
ATOM	1990	N	GLY	A	208	102.083	20.328	23.418	1.00 28.50
ATOM	1992	CA	GLY	A	208	103.112	19.330	23.194	1.00 29.80
ATOM	1993	C	GLY	A	208	103.130	18.752	21.795	1.00 32.56
ATOM	1994	O	GLY	A	208	102.067	18.467	21.231	1.00 33.45
ATOM	1995	N	LEU	A	209	104.332	18.598	21.235	1.00 33.15
ATOM	1997	CA	LEU	A	209	104.512	18.038	19.899	1.00 31.79
ATOM	1998	CB	LEU	A	209	105.985	18.081	19.484	1.00 29.49

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ATOM	1999	CG	LEU A 209	106.491	19.337	18.773	1.00	28.06
ATOM	2000	CD1	LEU A 209	106.302	20.558	19.641	1.00	24.35
ATOM	2001	CD2	LEU A 209	107.953	19.158	18.416	1.00	24.06
ATOM	2002	C	LEU A 209	104.052	16.599	19.941	1.00	31.52
ATOM	2003	O	LEU A 209	104.416	15.863	20.854	1.00	33.82
ATOM	2004	N	VAL A 210	103.254	16.199	18.961	1.00	29.87
ATOM	2006	CA	VAL A 210	102.752	14.836	18.915	1.00	29.99
ATOM	2007	CB	VAL A 210	101.226	14.817	18.732	1.00	30.37
ATOM	2008	CG1	VAL A 210	100.559	15.363	19.972	1.00	31.24
ATOM	2009	CG2	VAL A 210	100.824	15.642	17.522	1.00	30.83
ATOM	2010	C	VAL A 210	103.430	13.992	17.837	1.00	30.78
ATOM	2011	O	VAL A 210	103.038	12.854	17.578	1.00	32.27
ATOM	2012	N	ALA A 211	104.460	14.552	17.221	1.00	30.97
ATOM	2014	CA	ALA A 211	105.199	13.857	16.178	1.00	32.26
ATOM	2015	CB	ALA A 211	104.324	13.661	14.941	1.00	34.28
ATOM	2016	C	ALA A 211	106.417	14.692	15.839	1.00	31.64
ATOM	2017	O	ALA A 211	106.463	15.884	16.145	1.00	32.86
ATOM	2018	N	PRO A 212	107.437	14.077	15.232	1.00	30.38
ATOM	2019	CD	PRO A 212	107.550	12.667	14.820	1.00	28.87
ATOM	2020	CA	PRO A 212	108.642	14.824	14.876	1.00	30.59
ATOM	2021	CB	PRO A 212	109.576	13.724	14.384	1.00	30.90
ATOM	2022	CG	PRO A 212	108.628	12.731	13.785	1.00	31.64
ATOM	2023	C	PRO A 212	108.345	15.824	13.774	1.00	31.31
ATOM	2024	O	PRO A 212	107.483	15.574	12.938	1.00	33.01
ATOM	2025	N	PRO A 213	109.005	16.996	13.802	1.00	30.25
ATOM	2026	CD	PRO A 213	109.882	17.457	14.892	1.00	28.21
ATOM	2027	CA	PRO A 213	108.832	18.056	12.803	1.00	29.74
ATOM	2028	CB	PRO A 213	109.889	19.076	13.220	1.00	29.54
ATOM	2029	CG	PRO A 213	109.896	18.958	14.690	1.00	26.77
ATOM	2030	C	PRO A 213	109.115	17.526	11.398	1.00	30.72
ATOM	2031	O	PRO A 213	110.187	16.975	11.140	1.00	33.55
ATOM	2032	N	ALA A 214	108.157	17.700	10.495	1.00	30.16
ATOM	2034	CA	ALA A 214	108.296	17.231	9.123	1.00	29.31
ATOM	2035	CB	ALA A 214	106.964	16.701	8.609	1.00	27.36

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ATOM	2036	C	ALA	A	214	108.771	18.336	8.212	1.00 30.52
ATOM	2037	O	ALA	A	214	108.229	19.440	8.235	1.00 32.72
ATOM	2038	N	THR	A	215	109.781	18.052	7.405	1.00 30.13
ATOM	2040	CA	THR	A	215	110.268	19.047	6.472	1.00 31.47
ATOM	2041	CB	THR	A	215	111.805	19.044	6.366	1.00 32.14
ATOM	2042	OG1	THR	A	215	112.381	19.228	7.665	1.00 36.33
ATOM	2044	CG2	THR	A	215	112.268	20.177	5.474	1.00 33.34
ATOM	2045	C	THR	A	215	109.656	18.698	5.127	1.00 32.34
ATOM	2046	O	THR	A	215	109.642	17.533	4.729	1.00 32.18
ATOM	2047	N	THR	A	216	109.103	19.692	4.451	1.00 34.34
ATOM	2049	CA	THR	A	216	108.489	19.463	3.154	1.00 36.27
ATOM	2050	CB	THR	A	216	106.996	19.862	3.167	1.00 36.83
ATOM	2051	OG1	THR	A	216	106.872	21.255	3.477	1.00 37.89
ATOM	2053	CG2	THR	A	216	106.241	19.055	4.216	1.00 36.73
ATOM	2054	C	THR	A	216	109.247	20.254	2.092	1.00 37.93
ATOM	2055	O	THR	A	216	110.390	20.642	2.307	1.00 36.96
ATOM	2056	N	ALA	A	217	108.610	20.483	0.948	1.00 40.73
ATOM	2058	CA	ALA	A	217	109.228	21.215	-0.151	1.00 41.25
ATOM	2059	CB	ALA	A	217	108.452	20.967	-1.437	1.00 42.73
ATOM	2060	C	ALA	A	217	109.302	22.704	0.125	1.00 40.38
ATOM	2061	O	ALA	A	217	110.218	23.379	-0.337	1.00 40.36
ATOM	2062	N	GLU	A	218	108.319	23.215	0.860	1.00 41.20
ATOM	2064	CA	GLU	A	218	108.271	24.633	1.170	1.00 40.88
ATOM	2065	CB	GLU	A	218	107.443	25.372	0.113	1.00 46.00
ATOM	2066	CG	GLU	A	218	108.304	26.058	-0.947	1.00 53.45
ATOM	2067	CD	GLU	A	218	107.610	26.213	-2.286	1.00 57.50
ATOM	2068	OE1	GLU	A	218	106.543	25.588	-2.487	1.00 60.01
ATOM	2069	OE2	GLU	A	218	108.149	26.945	-3.146	1.00 59.32
ATOM	2070	C	GLU	A	218	107.832	25.030	2.580	1.00 39.13
ATOM	2071	O	GLU	A	218	107.635	26.216	2.839	1.00 40.54
ATOM	2072	N	THR	A	219	107.668	24.066	3.488	1.00 37.20
ATOM	2074	CA	THR	A	219	107.295	24.388	4.875	1.00 35.55
ATOM	2075	CB	THR	A	219	105.762	24.464	5.103	1.00 32.68

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ATOM	2076	OG1	THR	A	219	105.144	23.249	4.674	1.00 35.48
ATOM	2078	CG2	THR	A	219	105.151	25.641	4.387	1.00 33.81
ATOM	2079	C	THR	A	219	107.828	23.400	5.906	1.00 34.31
ATOM	2080	O	THR	A	219	108.013	22.217	5.614	1.00 34.57
ATOM	2081	N	LEU	A	220	108.087	23.903	7.109	1.00 31.67
ATOM	2083	CA	LEU	A	220	108.533	23.079	8.219	1.00 29.70
ATOM	2084	CB	LEU	A	220	109.587	23.834	9.033	1.00 29.62
ATOM	2085	CG	LEU	A	220	110.345	23.149	10.177	1.00 31.10
ATOM	2086	CD1	LEU	A	220	109.511	23.047	11.435	1.00 30.08
ATOM	2087	CD2	LEU	A	220	110.794	21.791	9.727	1.00 30.78
ATOM	2088	C	LEU	A	220	107.236	22.902	9.017	1.00 29.78
ATOM	2089	O	LEU	A	220	106.693	23.878	9.545	1.00 30.49
ATOM	2090	N	ASP	A	221	106.698	21.685	9.032	1.00 29.15
ATOM	2092	CA	ASP	A	221	105.441	21.397	9.728	1.00 30.48
ATOM	2093	CB	ASP	A	221	104.603	20.394	8.924	1.00 34.57
ATOM	2094	CG	ASP	A	221	104.178	20.924	7.557	1.00 37.91
ATOM	2095	OD1	ASP	A	221	104.480	22.090	7.222	1.00 37.84
ATOM	2096	OD2	ASP	A	221	103.534	20.158	6.811	1.00 42.30
ATOM	2097	C	ASP	A	221	105.607	20.865	11.143	1.00 30.64
ATOM	2098	O	ASP	A	221	106.274	19.852	11.350	1.00 31.22
ATOM	2099	N	VAL	A	222	104.950	21.519	12.100	1.00 29.81
ATOM	2101	CA	VAL	A	222	104.999	21.131	13.512	1.00 29.49
ATOM	2102	CB	VAL	A	222	105.588	22.261	14.389	1.00 29.52
ATOM	2103	CG1	VAL	A	222	105.617	21.831	15.845	1.00 28.17
ATOM	2104	CG2	VAL	A	222	106.988	22.632	13.914	1.00 26.55
ATOM	2105	C	VAL	A	222	103.586	20.791	14.016	1.00 29.65
ATOM	2106	O	VAL	A	222	102.686	21.620	13.958	1.00 31.27
ATOM	2107	N	GLN	A	223	103.400	19.560	14.485	1.00 29.35
ATOM	2109	CA	GLN	A	223	102.114	19.081	14.978	1.00 25.88
ATOM	2110	CB	GLN	A	223	101.870	17.649	14.488	1.00 29.16
ATOM	2111	CG	GLN	A	223	101.731	17.505	12.969	1.00 30.27
ATOM	2112	CD	GLN	A	223	101.704	16.052	12.510	1.00 32.10
ATOM	2113	OE1	GLN	A	223	100.832	15.275	12.897	1.00 31.46
ATOM	2114	NE2	GLN	A	223	102.668	15.681	11.686	1.00 37.75

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ATOM	2117	C	GLN A 223	102.081	19.116	16.494	1.00	24.57
ATOM	2118	O	GLN A 223	102.910	18.490	17.147	1.00	23.51
ATOM	2119	N	MET A 224	101.112	19.840	17.042	1.00	22.94
ATOM	2121	CA	MET A 224	100.959	19.984	18.480	1.00	22.16
ATOM	2122	CB	MET A 224	101.064	21.459	18.866	1.00	23.89
ATOM	2123	CG	MET A 224	102.353	22.116	18.423	1.00	22.07
ATOM	2124	SD	MET A 224	102.393	23.853	18.797	1.00	28.37
ATOM	2125	CE	MET A 224	104.122	24.130	18.771	1.00	25.60
ATOM	2126	C	MET A 224	99.620	19.408	18.927	1.00	23.31
ATOM	2127	O	MET A 224	98.702	19.294	18.124	1.00	27.48
ATOM	2128	N	LYS A 225	99.519	19.024	20.197	1.00	25.28
ATOM	2130	CA	LYS A 225	98.292	18.440	20.735	1.00	27.30
ATOM	2131	CB	LYS A 225	98.522	17.889	22.140	1.00	28.45
ATOM	2132	CG	LYS A 225	97.613	16.724	22.452	1.00	30.88
ATOM	2133	CD	LYS A 225	97.912	16.108	23.793	1.00	33.18
ATOM	2134	CE	LYS A 225	97.153	14.802	23.938	1.00	38.68
ATOM	2135	NZ	LYS A 225	95.741	14.928	23.460	1.00	43.39
ATOM	2139	C	LYS A 225	97.135	19.434	20.726	1.00	27.30
ATOM	2140	O	LYS A 225	96.052	19.123	20.238	1.00	29.51
ATOM	2141	N	GLY A 226	97.364	20.617	21.286	1.00	26.18
ATOM	2143	CA	GLY A 226	96.360	21.665	21.285	1.00	21.95
ATOM	2144	C	GLY A 226	95.015	21.379	21.903	1.00	23.48
ATOM	2145	O	GLY A 226	93.983	21.420	21.238	1.00	23.78
ATOM	2146	N	GLU A 227	95.021	21.131	23.201	1.00	26.02
ATOM	2148	CA	GLU A 227	93.792	20.882	23.915	1.00	26.24
ATOM	2149	CB	GLU A 227	93.547	19.384	24.068	1.00	29.17
ATOM	2150	CG	GLU A 227	94.467	18.697	25.052	1.00	25.81
ATOM	2151	CD	GLU A 227	93.967	17.330	25.456	1.00	29.15
ATOM	2152	OE1	GLU A 227	93.343	16.654	24.614	1.00	33.43
ATOM	2153	OE2	GLU A 227	94.199	16.928	26.615	1.00	31.54
ATOM	2154	C	GLU A 227	93.937	21.514	25.283	1.00	27.06
ATOM	2155	O	GLU A 227	95.006	21.447	25.892	1.00	26.79
ATOM	2156	N	PHE A 228	92.904	22.219	25.722	1.00	26.37

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ATOM	2158	CA	PHE	A	228	92.942	22.816	27.034	1.00 24.07
ATOM	2159	CB	PHE	A	228	91.785	23.792	27.242	1.00 24.55
ATOM	2160	CG	PHE	A	228	91.987	25.134	26.592	1.00 23.72
ATOM	2161	CD1	PHE	A	228	92.066	25.251	25.207	1.00 21.59
ATOM	2162	CD2	PHE	A	228	92.045	26.287	27.366	1.00 21.39
ATOM	2163	CE1	PHE	A	228	92.193	26.498	24.607	1.00 21.74
ATOM	2164	CE2	PHE	A	228	92.172	27.531	26.779	1.00 21.24
ATOM	2165	CZ	PHE	A	228	92.246	27.640	25.395	1.00 24.55
ATOM	2166	C	PHE	A	228	92.779	21.630	27.949	1.00 25.56
ATOM	2167	O	PHE	A	228	92.069	20.680	27.624	1.00 26.15
ATOM	2168	N	TYR	A	229	93.479	21.655	29.067	1.00 29.13
ATOM	2170	CA	TYR	A	229	93.400	20.573	30.025	1.00 34.87
ATOM	2171	CB	TYR	A	229	94.735	19.820	30.084	1.00 32.93
ATOM	2172	CG	TYR	A	229	95.870	20.654	30.639	1.00 33.77
ATOM	2173	CD1	TYR	A	229	96.034	20.816	32.015	1.00 34.08
ATOM	2174	CE1	TYR	A	229	97.021	21.637	32.530	1.00 33.96
ATOM	2175	CD2	TYR	A	229	96.739	21.332	29.793	1.00 34.25
ATOM	2176	CE2	TYR	A	229	97.735	22.152	30.302	1.00 34.53
ATOM	2177	CZ	TYR	A	229	97.863	22.302	31.670	1.00 33.54
ATOM	2178	OH	TYR	A	229	98.819	23.138	32.185	1.00 38.50
ATOM	2180	C	TYR	A	229	93.097	21.196	31.380	1.00 39.53
ATOM	2181	O	TYR	A	229	93.192	22.414	31.545	1.00 39.55
ATOM	2182	N	SER	A	230	92.738	20.355	32.341	1.00 46.28
ATOM	2184	CA	SER	A	230	92.453	20.796	33.699	1.00 53.45
ATOM	2185	CB	SER	A	230	90.998	20.491	34.071	1.00 54.47
ATOM	2186	OG	SER	A	230	90.720	20.820	35.424	1.00 56.07
ATOM	2188	C	SER	A	230	93.396	19.996	34.582	1.00 58.48
ATOM	2189	O	SER	A	230	93.659	18.826	34.301	1.00 58.09
ATOM	2190	N	GLU	A	231	93.946	20.632	35.611	1.00 66.92
ATOM	2192	CA	GLU	A	231	94.860	19.940	36.517	1.00 74.85
ATOM	2193	CB	GLU	A	231	95.976	20.878	36.995	1.00 77.02
ATOM	2194	CG	GLU	A	231	97.377	20.450	36.548	1.00 81.62
ATOM	2195	CD	GLU	A	231	98.476	21.372	37.054	1.00 84.67
ATOM	2196	OE1	GLU	A	231	98.402	22.592	36.790	1.00 86.64

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ATOM	2197	OE2	GLU A 231	99.421	20.876	37.709	1.00	85.89
ATOM	2198	C	GLU A 231	94.119	19.328	37.706	1.00	78.17
ATOM	2199	O	GLU A 231	94.602	18.379	38.323	1.00	79.46
ATOM	2200	N	ALA A 232	92.934	19.855	38.003	1.00	81.24
ATOM	2202	CA	ALA A 232	92.131	19.363	39.118	1.00	84.16
ATOM	2203	CB	ALA A 232	91.111	20.417	39.544	1.00	84.14
ATOM	2204	C	ALA A 232	91.426	18.053	38.777	1.00	86.04
ATOM	2205	O	ALA A 232	91.078	17.279	39.671	1.00	87.55
ATOM	2206	N	ALA A 233	91.203	17.819	37.487	1.00	86.79
ATOM	2208	CA	ALA A 233	90.534	16.608	37.023	1.00	88.81
ATOM	2209	CB	ALA A 233	89.052	16.659	37.381	1.00	89.87
ATOM	2210	C	ALA A 233	90.702	16.464	35.516	1.00	90.03
ATOM	2211	O	ALA A 233	90.288	17.341	34.756	1.00	90.77
ATOM	2212	N	ALA A 234	91.309	15.361	35.090	1.00	91.16
ATOM	2214	CA	ALA A 234	91.536	15.106	33.670	1.00	91.66
ATOM	2215	CB	ALA A 234	92.810	14.288	33.470	1.00	92.37
ATOM	2216	C	ALA A 234	90.354	14.394	33.034	1.00	91.31
ATOM	2217	O	ALA A 234	89.874	13.384	33.550	1.00	91.09
ATOM	2218	N	ALA A 235	89.894	14.926	31.908	1.00	91.34
ATOM	2220	CA	ALA A 235	88.774	14.346	31.180	1.00	90.88
ATOM	2221	CB	ALA A 235	87.457	14.975	31.627	1.00	91.57
ATOM	2222	C	ALA A 235	88.993	14.572	29.691	1.00	89.83
ATOM	2223	O	ALA A 235	89.205	15.706	29.247	1.00	89.77
ATOM	2224	N	PRO A 236	89.032	13.480	28.912	1.00	88.56
ATOM	2225	CD	PRO A 236	88.962	12.083	29.376	1.00	88.69
ATOM	2226	CA	PRO A 236	89.232	13.539	27.463	1.00	85.91
ATOM	2227	CB	PRO A 236	89.511	12.080	27.104	1.00	86.56
ATOM	2228	CG	PRO A 236	88.680	11.334	28.099	1.00	88.16
ATOM	2229	C	PRO A 236	87.997	14.085	26.738	1.00	82.58
ATOM	2230	O	PRO A 236	86.861	13.877	27.172	1.00	81.75
ATOM	2231	N	PRO A 237	88.217	14.829	25.644	1.00	79.77
ATOM	2232	CD	PRO A 237	89.551	15.264	25.202	1.00	80.44
ATOM	2233	CA	PRO A 237	87.178	15.444	24.811	1.00	77.34

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ATOM	2234	CB	PRO A 237	87.985	16.332	23.863	1.00	77.69
ATOM	2235	CG	PRO A 237	89.249	16.604	24.617	1.00	79.85
ATOM	2236	C	PRO A 237	86.366	14.426	24.015	1.00	75.23
ATOM	2237	O	PRO A 237	86.919	13.462	23.480	1.00	75.90
ATOM	2238	N	PRO A 238	85.042	14.634	23.918	1.00	72.71
ATOM	2239	CD	PRO A 238	84.282	15.606	24.724	1.00	72.84
ATOM	2240	CA	PRO A 238	84.131	13.750	23.182	1.00	70.12
ATOM	2241	CB	PRO A 238	82.774	14.086	23.793	1.00	71.89
ATOM	2242	CG	PRO A 238	82.907	15.535	24.109	1.00	72.51
ATOM	2243	C	PRO A 238	84.146	14.004	21.672	1.00	67.49
ATOM	2244	O	PRO A 238	83.099	14.016	21.017	1.00	66.70
ATOM	2245	N	PHE A 239	85.340	14.216	21.130	1.00	64.79
ATOM	2247	CA	PHE A 239	85.521	14.472	19.706	1.00	61.01
ATOM	2248	CB	PHE A 239	84.959	15.849	19.319	1.00	60.29
ATOM	2249	CG	PHE A 239	85.172	16.923	20.362	1.00	57.87
ATOM	2250	CD1	PHE A 239	86.307	17.721	20.339	1.00	56.42
ATOM	2251	CD2	PHE A 239	84.216	17.159	21.343	1.00	55.75
ATOM	2252	CE1	PHE A 239	86.484	18.737	21.274	1.00	53.82
ATOM	2253	CE2	PHE A 239	84.387	18.171	22.279	1.00	53.85
ATOM	2254	CZ	PHE A 239	85.522	18.960	22.243	1.00	52.72
ATOM	2255	C	PHE A 239	86.989	14.355	19.307	1.00	58.61
ATOM	2256	O	PHE A 239	87.873	14.266	20.164	1.00	58.11
ATOM	2257	N	ALA A 240	87.234	14.314	18.002	1.00	55.15
ATOM	2259	CA	ALA A 240	88.586	14.203	17.472	1.00	51.42
ATOM	2260	CB	ALA A 240	88.716	12.936	16.631	1.00	51.91
ATOM	2261	C	ALA A 240	88.884	15.441	16.629	1.00	49.88
ATOM	2262	O	ALA A 240	87.972	16.034	16.048	1.00	48.56
ATOM	2263	N	PRO A 241	90.155	15.885	16.604	1.00	48.54
ATOM	2264	CD	PRO A 241	91.270	15.398	17.436	1.00	47.09
ATOM	2265	CA	PRO A 241	90.567	17.064	15.830	1.00	46.53
ATOM	2266	CB	PRO A 241	92.043	17.218	16.205	1.00	44.66
ATOM	2267	CG	PRO A 241	92.113	16.633	17.574	1.00	45.79
ATOM	2268	C	PRO A 241	90.412	16.864	14.322	1.00	46.25
ATOM	2269	O	PRO A 241	90.536	15.743	13.819	1.00	47.76

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ATOM	2270	N	PRO	A	242	90.118	17.947	13.582	1.00 45.32
ATOM	2271	CD	PRO	A	242	89.818	19.314	14.050	1.00 44.47
ATOM	2272	CA	PRO	A	242	89.959	17.844	12.130	1.00 44.33
ATOM	2273	CB	PRO	A	242	89.187	19.114	11.792	1.00 43.70
ATOM	2274	CG	PRO	A	242	89.769	20.107	12.755	1.00 43.85
ATOM	2275	C	PRO	A	242	91.325	17.835	11.442	1.00 45.10
ATOM	2276	O	PRO	A	242	92.331	18.261	12.019	1.00 44.03
ATOM	2277	N	VAL	A	243	91.370	17.302	10.228	1.00 45.79
ATOM	2279	CA	VAL	A	243	92.615	17.279	9.485	1.00 47.91
ATOM	2280	CB	VAL	A	243	92.613	16.226	8.347	1.00 48.72
ATOM	2281	CG1	VAL	A	243	92.629	14.827	8.934	1.00 50.59
ATOM	2282	CG2	VAL	A	243	91.403	16.401	7.446	1.00 51.20
ATOM	2283	C	VAL	A	243	92.753	18.679	8.926	1.00 48.35
ATOM	2284	O	VAL	A	243	91.939	19.122	8.116	1.00 48.79
ATOM	2285	N	MET	A	244	93.731	19.412	9.434	1.00 48.68
ATOM	2287	CA	MET	A	244	93.937	20.771	8.987	1.00 46.91
ATOM	2288	CB	MET	A	244	94.406	21.638	10.147	1.00 42.52
ATOM	2289	CG	MET	A	244	93.369	21.770	11.233	1.00 30.61
ATOM	2290	SD	MET	A	244	93.963	22.834	12.505	1.00 30.25
ATOM	2291	CE	MET	A	244	94.948	21.710	13.447	1.00 25.62
ATOM	2292	C	MET	A	244	94.884	20.877	7.811	1.00 50.14
ATOM	2293	O	MET	A	244	96.102	20.935	7.983	1.00 50.38
ATOM	2294	N	GLU	A	245	94.302	20.867	6.615	1.00 53.76
ATOM	2296	CA	GLU	A	245	95.046	20.985	5.367	1.00 58.60
ATOM	2297	CB	GLU	A	245	94.597	19.905	4.364	1.00 61.51
ATOM	2298	CG	GLU	A	245	93.085	19.861	4.078	1.00 67.59
ATOM	2299	CD	GLU	A	245	92.692	18.811	3.041	1.00 69.79
ATOM	2300	OE1	GLU	A	245	92.943	19.024	1.827	1.00 72.17
ATOM	2301	OE2	GLU	A	245	92.104	17.778	3.439	1.00 68.95
ATOM	2302	C	GLU	A	245	94.817	22.382	4.794	1.00 59.59
ATOM	2303	O	GLU	A	245	93.765	22.664	4.220	1.00 60.79
ATOM	2304	N	PHE	A	246	95.773	23.278	5.010	1.00 61.44
ATOM	2306	CA	PHE	A	246	95.637	24.635	4.510	1.00 63.27

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ATOM	2307	CB	PHE A 246	95.567	25.658	5.657	1.00	60.46
ATOM	2308	CG	PHE A 246	96.689	25.567	6.663	1.00	56.43
ATOM	2309	CD1	PHE A 246	97.850	26.319	6.502	1.00	54.28
ATOM	2310	CD2	PHE A 246	96.532	24.825	7.834	1.00	53.72
ATOM	2311	CE1	PHE A 246	98.829	26.342	7.497	1.00	51.24
ATOM	2312	CE2	PHE A 246	97.506	24.841	8.834	1.00	51.21
ATOM	2313	CZ	PHE A 246	98.653	25.602	8.667	1.00	48.89
ATOM	2314	C	PHE A 246	96.676	25.022	3.473	1.00	67.53
ATOM	2315	O	PHE A 246	97.723	24.382	3.357	1.00	68.37
ATOM	2316	N	PRO A 247	96.375	26.050	2.664	1.00	71.27
ATOM	2317	CD	PRO A 247	95.153	26.874	2.673	1.00	72.37
ATOM	2318	CA	PRO A 247	97.297	26.511	1.624	1.00	74.18
ATOM	2319	CB	PRO A 247	96.504	27.627	0.938	1.00	74.64
ATOM	2320	CG	PRO A 247	95.626	28.147	2.038	1.00	73.71
ATOM	2321	C	PRO A 247	98.620	27.016	2.180	1.00	76.26
ATOM	2322	O	PRO A 247	98.661	28.002	2.920	1.00	76.91
ATOM	2323	N	ALA A 248	99.691	26.299	1.858	1.00	78.37
ATOM	2325	CA	ALA A 248	101.027	26.675	2.298	1.00	80.34
ATOM	2326	CB	ALA A 248	102.025	25.578	1.963	1.00	80.57
ATOM	2327	C	ALA A 248	101.385	27.950	1.556	1.00	81.06
ATOM	2328	O	ALA A 248	101.463	27.962	0.325	1.00	81.92
ATOM	2329	N	ALA A 249	101.564	29.030	2.300	1.00	80.72
ATOM	2331	CA	ALA A 249	101.902	30.303	1.694	1.00	79.65
ATOM	2332	CB	ALA A 249	100.799	31.319	1.964	1.00	80.65
ATOM	2333	C	ALA A 249	103.232	30.799	2.234	1.00	78.22
ATOM	2334	O	ALA A 249	103.799	30.201	3.150	1.00	78.60
ATOM	2335	N	ALA A 250	103.734	31.878	1.643	1.00	76.27
ATOM	2337	CA	ALA A 250	104.997	32.476	2.062	1.00	74.32
ATOM	2338	CB	ALA A 250	106.093	32.174	1.042	1.00	75.66
ATOM	2339	C	ALA A 250	104.840	33.985	2.249	1.00	71.97
ATOM	2340	O	ALA A 250	105.815	34.732	2.160	1.00	72.98
ATOM	2341	N	ASP A 251	103.606	34.422	2.496	1.00	67.46
ATOM	2343	CA	ASP A 251	103.302	35.836	2.708	1.00	61.94
ATOM	2344	CB	ASP A 251	101.797	36.090	2.568	1.00	66.00

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ATOM	2345	CG	ASP	A	251	101.277	35.785	1.177	1.00 70.21
ATOM	2346	OD1	ASP	A	251	101.467	34.647	0.695	1.00 71.96
ATOM	2347	OD2	ASP	A	251	100.668	36.687	0.566	1.00 72.84
ATOM	2348	C	ASP	A	251	103.760	36.265	4.101	1.00 56.10
ATOM	2349	O	ASP	A	251	104.203	37.396	4.298	1.00 56.97
ATOM	2350	N	ARG	A	252	103.611	35.364	5.067	1.00 47.53
ATOM	2352	CA	ARG	A	252	104.009	35.622	6.441	1.00 39.41
ATOM	2353	CB	ARG	A	252	102.815	35.472	7.384	1.00 39.71
ATOM	2354	CG	ARG	A	252	101.668	36.426	7.129	1.00 39.66
ATOM	2355	CD	ARG	A	252	101.975	37.837	7.596	1.00 41.34
ATOM	2356	NE	ARG	A	252	100.830	38.714	7.375	1.00 42.20
ATOM	2358	CZ	ARG	A	252	100.628	39.416	6.263	1.00 44.51
ATOM	2359	NH1	ARG	A	252	101.498	39.358	5.263	1.00 45.26
ATOM	2362	NH2	ARG	A	252	99.542	40.163	6.141	1.00 44.83
ATOM	2365	C	ARG	A	252	105.070	34.594	6.798	1.00 34.91
ATOM	2366	O	ARG	A	252	105.315	33.667	6.035	1.00 31.70
ATOM	2367	N	MET	A	253	105.662	34.730	7.976	1.00 32.83
ATOM	2369	CA	MET	A	253	106.697	33.809	8.417	1.00 30.84
ATOM	2370	CB	MET	A	253	107.605	34.499	9.441	1.00 30.27
ATOM	2371	CG	MET	A	253	108.192	35.807	8.925	1.00 31.26
ATOM	2372	SD	MET	A	253	109.366	36.637	10.009	1.00 34.11
ATOM	2373	CE	MET	A	253	110.335	37.492	8.834	1.00 29.80
ATOM	2374	C	MET	A	253	106.130	32.501	8.979	1.00 31.42
ATOM	2375	O	MET	A	253	106.568	31.419	8.595	1.00 31.42
ATOM	2376	N	VAL	A	254	105.144	32.600	9.866	1.00 31.26
ATOM	2378	CA	VAL	A	254	104.540	31.419	10.480	1.00 32.17
ATOM	2379	CB	VAL	A	254	104.781	31.376	12.015	1.00 32.83
ATOM	2380	CG1	VAL	A	254	106.243	31.143	12.324	1.00 35.48
ATOM	2381	CG2	VAL	A	254	104.316	32.672	12.658	1.00 33.43
ATOM	2382	C	VAL	A	254	103.043	31.378	10.262	1.00 32.00
ATOM	2383	O	VAL	A	254	102.412	32.410	10.059	1.00 33.43
ATOM	2384	N	TYR	A	255	102.478	30.181	10.340	1.00 33.42
ATOM	2386	CA	TYR	A	255	101.044	29.979	10.179	1.00 32.60

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ATOM	2387	CB	TYR	A	255	100.726	29.448	8.784	1.00 32.98
ATOM	2388	CG	TYR	A	255	100.746	30.482	7.694	1.00 32.36
ATOM	2389	CD1	TYR	A	255	101.913	30.756	6.987	1.00 31.99
ATOM	2390	CE1	TYR	A	255	101.921	31.674	5.947	1.00 33.10
ATOM	2391	CD2	TYR	A	255	99.587	31.154	7.335	1.00 31.03
ATOM	2392	CE2	TYR	A	255	99.583	32.072	6.298	1.00 32.21
ATOM	2393	CZ	TYR	A	255	100.750	32.325	5.607	1.00 33.29
ATOM	2394	OH	TYR	A	255	100.741	33.230	4.573	1.00 38.59
ATOM	2396	C	TYR	A	255	100.559	28.955	11.195	1.00 31.73
ATOM	2397	O	TYR	A	255	101.156	27.892	11.330	1.00 32.57
ATOM	2398	N	LEU	A	256	99.490	29.279	11.914	1.00 31.36
ATOM	2400	CA	LEU	A	256	98.916	28.370	12.893	1.00 29.13
ATOM	2401	CB	LEU	A	256	98.878	28.992	14.280	1.00 28.40
ATOM	2402	CG	LEU	A	256	100.206	29.125	15.014	1.00 28.89
ATOM	2403	CD1	LEU	A	256	101.045	30.208	14.375	1.00 32.20
ATOM	2404	CD2	LEU	A	256	99.938	29.462	16.471	1.00 32.12
ATOM	2405	C	LEU	A	256	97.509	27.984	12.489	1.00 30.86
ATOM	2406	O	LEU	A	256	96.748	28.814	11.987	1.00 30.77
ATOM	2407	N	GLY	A	257	97.203	26.701	12.652	1.00 31.62
ATOM	2409	CA	GLY	A	257	95.888	26.180	12.345	1.00 29.36
ATOM	2410	C	GLY	A	257	95.287	25.827	13.688	1.00 29.99
ATOM	2411	O	GLY	A	257	95.662	24.830	14.295	1.00 32.08
ATOM	2412	N	LEU	A	258	94.402	26.686	14.177	1.00 29.99
ATOM	2414	CA	LEU	A	258	93.742	26.507	15.463	1.00 26.58
ATOM	2415	CB	LEU	A	258	93.562	27.871	16.101	1.00 26.90
ATOM	2416	CG	LEU	A	258	94.866	28.668	16.049	1.00 28.57
ATOM	2417	CD1	LEU	A	258	94.583	30.144	16.176	1.00 29.14
ATOM	2418	CD2	LEU	A	258	95.808	28.177	17.139	1.00 29.78
ATOM	2419	C	LEU	A	258	92.397	25.838	15.253	1.00 28.27
ATOM	2420	O	LEU	A	258	91.404	26.499	14.936	1.00 29.90
ATOM	2421	N	SER	A	259	92.370	24.523	15.434	1.00 28.81
ATOM	2423	CA	SER	A	259	91.164	23.726	15.229	1.00 30.63
ATOM	2424	CB	SER	A	259	91.491	22.237	15.348	1.00 31.03
ATOM	2425	OG	SER	A	259	91.783	21.889	16.689	1.00 33.43

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ATOM	2427	C	SER	A	259	90.003	24.041	16.152	1.00 31.95
ATOM	2428	O	SER	A	259	90.184	24.600	17.231	1.00 33.18
ATOM	2429	N	ASP	A	260	88.808	23.637	15.729	1.00 32.89
ATOM	2431	CA	ASP	A	260	87.616	23.844	16.530	1.00 31.93
ATOM	2432	CB	ASP	A	260	86.326	23.521	15.739	1.00 33.23
ATOM	2433	CG	ASP	A	260	86.327	22.127	15.080	1.00 32.26
ATOM	2434	OD1	ASP	A	260	87.138	21.246	15.425	1.00 33.22
ATOM	2435	OD2	ASP	A	260	85.473	21.904	14.203	1.00 32.09
ATOM	2436	C	ASP	A	260	87.725	23.015	17.807	1.00 30.67
ATOM	2437	O	ASP	A	260	87.234	23.417	18.856	1.00 34.53
ATOM	2438	N	TYR	A	261	88.414	21.881	17.715	1.00 27.04
ATOM	2440	CA	TYR	A	261	88.629	20.983	18.847	1.00 26.39
ATOM	2441	CB	TYR	A	261	89.490	19.789	18.382	1.00 27.42
ATOM	2442	CG	TYR	A	261	90.064	18.885	19.463	1.00 26.82
ATOM	2443	CD1	TYR	A	261	91.304	19.157	20.038	1.00 29.26
ATOM	2444	CE1	TYR	A	261	91.855	18.318	21.006	1.00 30.93
ATOM	2445	CD2	TYR	A	261	89.386	17.745	19.886	1.00 26.82
ATOM	2446	CE2	TYR	A	261	89.927	16.898	20.853	1.00 28.99
ATOM	2447	CZ	TYR	A	261	91.163	17.194	21.408	1.00 32.15
ATOM	2448	OH	TYR	A	261	91.715	16.368	22.364	1.00 36.84
ATOM	2450	C	TYR	A	261	89.345	21.796	19.917	1.00 25.35
ATOM	2451	O	TYR	A	261	88.939	21.824	21.076	1.00 31.74
ATOM	2452	N	PHE	A	262	90.361	22.525	19.488	1.00 23.54
ATOM	2454	CA	PHE	A	262	91.151	23.361	20.368	1.00 21.85
ATOM	2455	CB	PHE	A	262	92.141	24.158	19.514	1.00 19.79
ATOM	2456	CG	PHE	A	262	92.923	25.184	20.275	1.00 20.92
ATOM	2457	CD1	PHE	A	262	93.830	24.806	21.253	1.00 22.00
ATOM	2458	CD2	PHE	A	262	92.761	26.536	20.002	1.00 20.09
ATOM	2459	CE1	PHE	A	262	94.558	25.759	21.943	1.00 19.37
ATOM	2460	CE2	PHE	A	262	93.488	27.497	20.693	1.00 18.46
ATOM	2461	CZ	PHE	A	262	94.386	27.107	21.660	1.00 18.18
ATOM	2462	C	PHE	A	262	90.244	24.290	21.165	1.00 21.70
ATOM	2463	O	PHE	A	262	90.236	24.266	22.391	1.00 22.47

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ATOM	2464	N	PHE	A	263	89.432	25.060	20.457	1.00 24.02
ATOM	2466	CA	PHE	A	263	88.522	26.014	21.079	1.00 23.57
ATOM	2467	CB	PHE	A	263	87.843	26.845	20.005	1.00 22.46
ATOM	2468	CG	PHE	A	263	88.783	27.712	19.241	1.00 21.39
ATOM	2469	CD1	PHE	A	263	89.462	28.740	19.870	1.00 25.06
ATOM	2470	CD2	PHE	A	263	88.982	27.510	17.887	1.00 23.84
ATOM	2471	CE1	PHE	A	263	90.326	29.555	19.159	1.00 26.31
ATOM	2472	CE2	PHE	A	263	89.843	28.319	17.169	1.00 25.34
ATOM	2473	CZ	PHE	A	263	90.514	29.345	17.804	1.00 25.18
ATOM	2474	C	PHE	A	263	87.457	25.378	21.933	1.00 25.63
ATOM	2475	O	PHE	A	263	87.103	25.892	22.992	1.00 29.04
ATOM	2476	N	ASN	A	264	86.926	24.264	21.463	1.00 27.70
ATOM	2478	CA	ASN	A	264	85.882	23.577	22.193	1.00 26.71
ATOM	2479	CB	ASN	A	264	85.136	22.617	21.278	1.00 26.91
ATOM	2480	CG	ASN	A	264	84.183	23.338	20.345	1.00 26.18
ATOM	2481	OD1	ASN	A	264	83.115	23.779	20.755	1.00 29.25
ATOM	2482	ND2	ASN	A	264	84.563	23.462	19.087	1.00 30.59
ATOM	2485	C	ASN	A	264	86.359	22.898	23.470	1.00 26.40
ATOM	2486	O	ASN	A	264	85.587	22.763	24.414	1.00 27.80
ATOM	2487	N	THR	A	265	87.628	22.498	23.527	1.00 26.30
ATOM	2489	CA	THR	A	265	88.154	21.880	24.748	1.00 24.34
ATOM	2490	CB	THR	A	265	89.572	21.298	24.559	1.00 24.55
ATOM	2491	OG1	THR	A	265	90.453	22.296	24.033	1.00 26.59
ATOM	2493	CG2	THR	A	265	89.532	20.129	23.619	1.00 21.96
ATOM	2494	C	THR	A	265	88.175	22.924	25.865	1.00 23.53
ATOM	2495	O	THR	A	265	88.045	22.602	27.041	1.00 26.65
ATOM	2496	N	ALA	A	266	88.309	24.186	25.483	1.00 24.00
ATOM	2498	CA	ALA	A	266	88.315	25.276	26.437	1.00 22.35
ATOM	2499	CB	ALA	A	266	88.582	26.590	25.723	1.00 21.75
ATOM	2500	C	ALA	A	266	86.956	25.310	27.113	1.00 23.18
ATOM	2501	O	ALA	A	266	86.865	25.297	28.336	1.00 27.51
ATOM	2502	N	GLY	A	267	85.897	25.286	26.311	1.00 24.69
ATOM	2504	CA	GLY	A	267	84.549	25.323	26.852	1.00 24.20
ATOM	2505	C	GLY	A	267	84.251	24.188	27.812	1.00 27.46

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ATOM	2506	O	GLY	A	267	83.637	24.381	28.869	1.00 27.80
ATOM	2507	N	LEU	A	268	84.699	22.997	27.445	1.00 28.36
ATOM	2509	CA	LEU	A	268	84.493	21.816	28.262	1.00 29.18
ATOM	2510	CB	LEU	A	268	84.996	20.580	27.520	1.00 32.75
ATOM	2511	CG	LEU	A	268	84.728	19.224	28.169	1.00 37.10
ATOM	2512	CD1	LEU	A	268	83.274	18.841	27.978	1.00 38.10
ATOM	2513	CD2	LEU	A	268	85.633	18.180	27.544	1.00 41.14
ATOM	2514	C	LEU	A	268	85.209	21.940	29.596	1.00 27.77
ATOM	2515	O	LEU	A	268	84.623	21.696	30.644	1.00 31.78
ATOM	2516	N	VAL	A	269	86.469	22.344	29.558	1.00 26.94
ATOM	2518	CA	VAL	A	269	87.256	22.478	30.774	1.00 26.89
ATOM	2519	CB	VAL	A	269	88.752	22.720	30.448	1.00 24.63
ATOM	2520	CG1	VAL	A	269	89.491	23.244	31.656	1.00 22.76
ATOM	2521	CG2	VAL	A	269	89.382	21.416	30.007	1.00 21.59
ATOM	2522	C	VAL	A	269	86.722	23.535	31.740	1.00 28.84
ATOM	2523	O	VAL	A	269	86.687	23.309	32.948	1.00 29.66
ATOM	2524	N	TYR	A	270	86.298	24.681	31.219	1.00 30.57
ATOM	2526	CA	TYR	A	270	85.769	25.734	32.080	1.00 28.60
ATOM	2527	CB	TYR	A	270	85.753	27.079	31.350	1.00 28.80
ATOM	2528	CG	TYR	A	270	87.111	27.734	31.265	1.00 27.47
ATOM	2529	CD1	TYR	A	270	87.766	28.169	32.415	1.00 25.23
ATOM	2530	CE1	TYR	A	270	89.021	28.754	32.343	1.00 26.36
ATOM	2531	CD2	TYR	A	270	87.750	27.906	30.038	1.00 29.53
ATOM	2532	CE2	TYR	A	270	89.008	28.494	29.959	1.00 25.30
ATOM	2533	CZ	TYR	A	270	89.632	28.912	31.114	1.00 24.84
ATOM	2534	OH	TYR	A	270	90.877	29.492	31.047	1.00 30.89
ATOM	2536	C	TYR	A	270	84.385	25.405	32.631	1.00 29.08
ATOM	2537	O	TYR	A	270	84.034	25.836	33.729	1.00 28.17
ATOM	2538	N	GLN	A	271	83.609	24.628	31.882	1.00 30.32
ATOM	2540	CA	GLN	A	271	82.269	24.249	32.316	1.00 29.24
ATOM	2541	CB	GLN	A	271	81.464	23.689	31.139	1.00 27.20
ATOM	2542	CG	GLN	A	271	79.957	23.680	31.357	1.00 27.60
ATOM	2543	CD	GLN	A	271	79.427	22.387	31.946	1.00 31.03

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ATOM	2544	OE1	GLN	A	271	79.982	21.306	31.724	1.00 35.11
ATOM	2545	NE2	GLN	A	271	78.318	22.484	32.668	1.00 28.89
ATOM	2548	C	GLN	A	271	82.329	23.226	33.438	1.00 30.41
ATOM	2549	O	GLN	A	271	81.839	23.473	34.539	1.00 32.81
ATOM	2550	N	GLU	A	272	82.976	22.098	33.168	1.00 33.61
ATOM	2552	CA	GLU	A	272	83.096	21.011	34.133	1.00 36.97
ATOM	2553	CB	GLU	A	272	83.807	19.822	33.492	1.00 40.58
ATOM	2554	CG	GLU	A	272	83.084	19.264	32.274	1.00 48.51
ATOM	2555	CD	GLU	A	272	83.781	18.051	31.674	1.00 55.01
ATOM	2556	OE1	GLU	A	272	84.998	18.129	31.405	1.00 59.64
ATOM	2557	OE2	GLU	A	272	83.112	17.016	31.468	1.00 57.25
ATOM	2558	C	GLU	A	272	83.761	21.376	35.460	1.00 36.60
ATOM	2559	O	GLU	A	272	83.674	20.622	36.425	1.00 40.35
ATOM	2560	N	ALA	A	273	84.429	22.522	35.512	1.00 35.77
ATOM	2562	CA	ALA	A	273	85.079	22.970	36.741	1.00 34.34
ATOM	2563	CB	ALA	A	273	86.316	23.798	36.418	1.00 32.87
ATOM	2564	C	ALA	A	273	84.104	23.778	37.594	1.00 34.54
ATOM	2565	O	ALA	A	273	84.459	24.252	38.679	1.00 35.72
ATOM	2566	N	GLY	A	274	82.879	23.930	37.086	1.00 35.04
ATOM	2568	CA	GLY	A	274	81.831	24.663	37.779	1.00 35.01
ATOM	2569	C	GLY	A	274	82.092	26.147	37.930	1.00 34.45
ATOM	2570	O	GLY	A	274	81.640	26.761	38.897	1.00 36.89
ATOM	2571	N	VAL	A	275	82.752	26.742	36.944	1.00 34.05
ATOM	2573	CA	VAL	A	275	83.083	28.157	37.018	1.00 34.43
ATOM	2574	CB	VAL	A	275	84.600	28.381	36.778	1.00 35.67
ATOM	2575	CG1	VAL	A	275	84.898	28.616	35.308	1.00 37.90
ATOM	2576	CG2	VAL	A	275	85.105	29.519	37.638	1.00 38.34
ATOM	2577	C	VAL	A	275	82.236	29.078	36.135	1.00 33.65
ATOM	2578	O	VAL	A	275	82.211	30.286	36.343	1.00 35.12
ATOM	2579	N	LEU	A	276	81.527	28.523	35.159	1.00 32.82
ATOM	2581	CA	LEU	A	276	80.683	29.352	34.307	1.00 29.38
ATOM	2582	CB	LEU	A	276	80.478	28.695	32.936	1.00 27.64
ATOM	2583	CG	LEU	A	276	81.739	28.482	32.082	1.00 25.37
ATOM	2584	CD1	LEU	A	276	81.370	27.883	30.757	1.00 24.34

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ATOM	2585	CD2	LEU	A	276	82.459	29.793	31.858	1.00 28.39
ATOM	2586	C	LEU	A	276	79.363	29.548	35.049	1.00 29.83
ATOM	2587	O	LEU	A	276	78.323	29.007	34.674	1.00 30.32
ATOM	2588	N	LYS	A	277	79.443	30.271	36.158	1.00 29.10
ATOM	2590	CA	LYS	A	277	78.294	30.546	37.004	1.00 27.79
ATOM	2591	CB	LYS	A	277	78.327	29.656	38.246	1.00 29.34
ATOM	2592	CG	LYS	A	277	78.211	28.183	37.956	1.00 33.13
ATOM	2593	CD	LYS	A	277	78.269	27.369	39.230	1.00 39.28
ATOM	2594	CE	LYS	A	277	78.064	25.888	38.930	1.00 44.23
ATOM	2595	NZ	LYS	A	277	78.321	25.022	40.119	1.00 46.99
ATOM	2599	C	LYS	A	277	78.386	32.002	37.420	1.00 26.55
ATOM	2600	O	LYS	A	277	79.474	32.556	37.516	1.00 28.05
ATOM	2601	N	MET	A	278	77.251	32.608	37.723	1.00 25.90
ATOM	2603	CA	MET	A	278	77.251	33.999	38.111	1.00 26.31
ATOM	2604	CB	MET	A	278	77.350	34.854	36.864	1.00 25.28
ATOM	2605	CG	MET	A	278	77.496	36.310	37.129	1.00 30.09
ATOM	2606	SD	MET	A	278	77.760	37.127	35.586	1.00 37.76
ATOM	2607	CE	MET	A	278	77.452	38.822	36.056	1.00 34.82
ATOM	2608	C	MET	A	278	75.985	34.338	38.872	1.00 28.79
ATOM	2609	O	MET	A	278	74.910	33.858	38.533	1.00 30.81
ATOM	2610	N	THR	A	279	76.123	35.134	39.925	1.00 30.03
ATOM	2612	CA	THR	A	279	74.987	35.544	40.728	1.00 29.69
ATOM	2613	CB	THR	A	279	75.242	35.277	42.211	1.00 29.00
ATOM	2614	OG1	THR	A	279	75.286	33.864	42.431	1.00 31.54
ATOM	2616	CG2	THR	A	279	74.140	35.863	43.060	1.00 28.67
ATOM	2617	C	THR	A	279	74.714	37.025	40.515	1.00 31.93
ATOM	2618	O	THR	A	279	75.615	37.856	40.644	1.00 32.91
ATOM	2619	N	LEU	A	280	73.482	37.338	40.128	1.00 33.14
ATOM	2621	CA	LEU	A	280	73.062	38.715	39.893	1.00 33.77
ATOM	2622	CB	LEU	A	280	72.268	38.826	38.581	1.00 34.16
ATOM	2623	CG	LEU	A	280	72.930	38.757	37.194	1.00 33.72
ATOM	2624	CD1	LEU	A	280	74.391	38.394	37.271	1.00 33.08
ATOM	2625	CD2	LEU	A	280	72.186	37.766	36.333	1.00 30.96

ATOM	2626	C	LEU	A	280	72.196	39.173	41.064	1.00 35.73
ATOM	2627	O	LEU	A	280	71.223	38.508	41.438	1.00 33.09
ATOM	2628	N	ARG	A	281	72.584	40.290	41.666	1.00 39.95
ATOM	2630	CA	ARG	A	281	71.864	40.860	42.796	1.00 42.55
ATOM	2631	CB	ARG	A	281	72.823	41.091	43.975	1.00 44.48
ATOM	2632	CG	ARG	A	281	73.472	39.824	44.534	1.00 47.55
ATOM	2633	CD	ARG	A	281	74.406	40.109	45.712	1.00 50.80
ATOM	2634	NE	ARG	A	281	75.660	40.757	45.321	1.00 57.47
ATOM	2636	CZ	ARG	A	281	76.844	40.145	45.263	1.00 61.45
ATOM	2637	NH1	ARG	A	281	76.956	38.852	45.552	1.00 62.83
ATOM	2640	NH2	ARG	A	281	77.925	40.825	44.901	1.00 62.95
ATOM	2643	C	ARG	A	281	71.255	42.190	42.354	1.00 44.72
ATOM	2644	O	ARG	A	281	71.782	42.854	41.458	1.00 46.61
ATOM	2645	N	ASP	A	282	70.179	42.601	43.014	1.00 46.42
ATOM	2647	CA	ASP	A	282	69.491	43.849	42.702	1.00 47.87
ATOM	2648	CB	ASP	A	282	68.284	44.039	43.634	1.00 49.38
ATOM	2649	CG	ASP	A	282	67.472	45.280	43.302	1.00 51.57
ATOM	2650	OD1	ASP	A	282	66.898	45.349	42.195	1.00 54.37
ATOM	2651	OD2	ASP	A	282	67.408	46.191	44.150	1.00 54.52
ATOM	2652	C	ASP	A	282	70.394	45.080	42.762	1.00 48.67
ATOM	2653	O	ASP	A	282	70.090	46.089	42.141	1.00 51.13
ATOM	2654	N	ASP	A	283	71.506	44.996	43.488	1.00 49.71
ATOM	2656	CA	ASP	A	283	72.427	46.128	43.608	1.00 50.78
ATOM	2657	CB	ASP	A	283	73.111	46.138	44.987	1.00 52.25
ATOM	2658	CG	ASP	A	283	73.994	44.920	45.224	1.00 55.58
ATOM	2659	OD1	ASP	A	283	75.189	44.953	44.847	1.00 58.60
ATOM	2660	OD2	ASP	A	283	73.498	43.935	45.810	1.00 58.13
ATOM	2661	C	ASP	A	283	73.474	46.236	42.492	1.00 51.35
ATOM	2662	O	ASP	A	283	74.362	47.086	42.543	1.00 52.74
ATOM	2663	N	MET	A	284	73.395	45.359	41.500	1.00 51.07
ATOM	2665	CA	MET	A	284	74.342	45.404	40.399	1.00 50.50
ATOM	2666	CB	MET	A	284	74.629	43.994	39.887	1.00 48.87
ATOM	2667	CG	MET	A	284	75.169	43.058	40.956	1.00 46.76
ATOM	2668	SD	MET	A	284	75.494	41.398	40.353	1.00 43.76

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ATOM	2669	CE	MET	A	284	76.804	40.895	41.457	1.00 47.06
ATOM	2670	C	MET	A	284	73.775	46.283	39.289	1.00 53.22
ATOM	2671	O	MET	A	284	74.515	46.824	38.466	1.00 55.85
ATOM	2672	N	ILE	A	285	72.455	46.433	39.285	1.00 55.37
ATOM	2674	CA	ILE	A	285	71.761	47.252	38.295	1.00 57.52
ATOM	2675	CB	ILE	A	285	70.287	46.792	38.141	1.00 55.38
ATOM	2676	CG2	ILE	A	285	69.583	47.611	37.070	1.00 56.70
ATOM	2677	CG1	ILE	A	285	70.235	45.303	37.783	1.00 53.28
ATOM	2678	CD1	ILE	A	285	68.838	44.723	37.732	1.00 50.41
ATOM	2679	C	ILE	A	285	71.787	48.707	38.776	1.00 59.50
ATOM	2680	O	ILE	A	285	71.358	48.998	39.889	1.00 60.66
ATOM	2681	N	PRO	A	286	72.304	49.635	37.951	1.00 61.05
ATOM	2682	CD	PRO	A	286	72.787	49.459	36.573	1.00 61.08
ATOM	2683	CA	PRO	A	286	72.360	51.048	38.350	1.00 62.59
ATOM	2684	CB	PRO	A	286	72.862	51.748	37.083	1.00 62.24
ATOM	2685	CG	PRO	A	286	72.481	50.801	35.974	1.00 63.04
ATOM	2686	C	PRO	A	286	71.004	51.583	38.817	1.00 64.15
ATOM	2687	O	PRO	A	286	69.986	51.400	38.154	1.00 63.39
ATOM	2688	N	LYS	A	287	71.016	52.268	39.956	1.00 67.25
ATOM	2690	CA	LYS	A	287	69.813	52.826	40.582	1.00 69.68
ATOM	2691	CB	LYS	A	287	70.204	53.622	41.838	1.00 72.51
ATOM	2692	CG	LYS	A	287	71.285	54.675	41.607	1.00 75.76
ATOM	2693	CD	LYS	A	287	71.483	55.570	42.826	1.00 78.18
ATOM	2694	CE	LYS	A	287	72.474	56.697	42.534	1.00 79.24
ATOM	2695	NZ	LYS	A	287	72.603	57.663	43.666	1.00 79.25
ATOM	2699	C	LYS	A	287	68.845	53.653	39.724	1.00 69.37
ATOM	2700	O	LYS	A	287	67.735	53.962	40.165	1.00 69.08
ATOM	2701	N	GLU	A	288	69.242	53.996	38.505	1.00 68.49
ATOM	2703	CA	GLU	A	288	68.386	54.792	37.635	1.00 69.17
ATOM	2704	CB	GLU	A	288	69.152	56.004	37.094	1.00 70.77
ATOM	2705	CG	GLU	A	288	69.897	56.826	38.142	1.00 73.92
ATOM	2706	CD	GLU	A	288	71.290	56.292	38.461	1.00 76.03
ATOM	2707	OE1	GLU	A	288	71.656	55.195	37.983	1.00 78.84

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ATOM	2708	OE2	GLU	A	288	72.031	56.981	39.196	1.00 76.47
ATOM	2709	C	GLU	A	288	67.851	53.965	36.469	1.00 68.68
ATOM	2710	O	GLU	A	288	68.012	54.345	35.310	1.00 70.05
ATOM	2711	N	SER	A	289	67.194	52.852	36.772	1.00 68.09
ATOM	2713	CA	SER	A	289	66.655	51.985	35.727	1.00 67.82
ATOM	2714	CB	SER	A	289	67.516	50.728	35.593	1.00 69.68
ATOM	2715	OG	SER	A	289	68.868	51.064	35.327	1.00 73.68
ATOM	2717	C	SER	A	289	65.202	51.590	35.977	1.00 66.67
ATOM	2718	O	SER	A	289	64.695	51.730	37.090	1.00 67.98
ATOM	2719	N	ALA	A	290	64.537	51.110	34.928	1.00 63.49
ATOM	2721	CA	ALA	A	290	63.144	50.691	35.027	1.00 60.33
ATOM	2722	CB	ALA	A	290	62.525	50.598	33.644	1.00 60.15
ATOM	2723	C	ALA	A	290	63.026	49.353	35.744	1.00 58.83
ATOM	2724	O	ALA	A	290	62.236	49.208	36.673	1.00 59.19
ATOM	2725	N	PHE	A	291	63.839	48.390	35.321	1.00 57.41
ATOM	2727	CA	PHE	A	291	63.829	47.043	35.894	1.00 55.46
ATOM	2728	CB	PHE	A	291	64.441	46.044	34.902	1.00 54.51
ATOM	2729	CG	PHE	A	291	63.658	45.890	33.622	1.00 52.78
ATOM	2730	CD1	PHE	A	291	62.493	45.130	33.588	1.00 52.76
ATOM	2731	CD2	PHE	A	291	64.085	46.505	32.451	1.00 52.05
ATOM	2732	CE1	PHE	A	291	61.760	44.983	32.414	1.00 51.50
ATOM	2733	CE2	PHE	A	291	63.360	46.364	31.270	1.00 52.10
ATOM	2734	CZ	PHE	A	291	62.194	45.601	31.255	1.00 51.58
ATOM	2735	C	PHE	A	291	64.519	46.912	37.260	1.00 53.52
ATOM	2736	O	PHE	A	291	65.541	47.547	37.524	1.00 53.59
ATOM	2737	N	ARG	A	292	63.966	46.046	38.104	1.00 50.17
ATOM	2739	CA	ARG	A	292	64.494	45.799	39.438	1.00 46.66
ATOM	2740	CB	ARG	A	292	63.677	46.562	40.481	1.00 46.93
ATOM	2741	CG	ARG	A	292	63.793	48.065	40.434	1.00 47.97
ATOM	2742	CD	ARG	A	292	64.964	48.536	41.256	1.00 49.34
ATOM	2743	NE	ARG	A	292	65.959	49.215	40.438	1.00 51.19
ATOM	2745	CZ	ARG	A	292	67.266	48.993	40.521	1.00 52.32
ATOM	2746	NH1	ARG	A	292	67.735	48.102	41.385	1.00 52.06
ATOM	2749	NH2	ARG	A	292	68.106	49.674	39.750	1.00 52.32

D0S4+5S4+5S4+5

ATOM	2752	C	ARG	A	292	64.317	44.322	39.715	1.00 46.15
ATOM	2753	O	ARG	A	292	63.333	43.720	39.278	1.00 47.65
ATOM	2754	N	LEU	A	293	65.278	43.725	40.409	1.00 44.69
ATOM	2756	CA	LEU	A	293	65.169	42.320	40.769	1.00 42.76
ATOM	2757	CB	LEU	A	293	66.546	41.648	40.819	1.00 37.95
ATOM	2758	CG	LEU	A	293	67.252	41.569	39.468	1.00 34.56
ATOM	2759	CD1	LEU	A	293	68.649	41.034	39.630	1.00 33.82
ATOM	2760	CD2	LEU	A	293	66.459	40.692	38.537	1.00 32.43
ATOM	2761	C	LEU	A	293	64.516	42.349	42.141	1.00 44.58
ATOM	2762	O	LEU	A	293	65.169	42.154	43.164	1.00 46.89
ATOM	2763	N	THR	A	294	63.239	42.716	42.150	1.00 44.93
ATOM	2765	CA	THR	A	294	62.453	42.804	43.370	1.00 45.20
ATOM	2766	CB	THR	A	294	62.220	44.271	43.781	1.00 44.99
ATOM	2767	OG1	THR	A	294	61.502	44.955	42.748	1.00 45.39
ATOM	2769	CG2	THR	A	294	63.547	44.983	44.012	1.00 46.79
ATOM	2770	C	THR	A	294	61.111	42.175	43.055	1.00 46.49
ATOM	2771	O	THR	A	294	60.639	42.269	41.922	1.00 48.98
ATOM	2772	N	THR	A	295	60.500	41.520	44.035	1.00 47.36
ATOM	2774	CA	THR	A	295	59.204	40.892	43.812	1.00 48.40
ATOM	2775	CB	THR	A	295	58.720	40.139	45.063	1.00 47.45
ATOM	2776	OG1	THR	A	295	58.837	40.986	46.210	1.00 47.38
ATOM	2778	CG2	THR	A	295	59.550	38.891	45.287	1.00 47.66
ATOM	2779	C	THR	A	295	58.179	41.952	43.410	1.00 49.59
ATOM	2780	O	THR	A	295	57.292	41.693	42.599	1.00 50.18
ATOM	2781	N	SER	A	296	58.347	43.157	43.950	1.00 51.29
ATOM	2783	CA	SER	A	296	57.468	44.288	43.667	1.00 52.78
ATOM	2784	CB	SER	A	296	57.978	45.538	44.390	1.00 54.54
ATOM	2785	OG	SER	A	296	57.219	46.688	44.056	1.00 55.48
ATOM	2787	C	SER	A	296	57.412	44.551	42.172	1.00 52.76
ATOM	2788	O	SER	A	296	56.340	44.532	41.562	1.00 52.27
ATOM	2789	N	PHE	A	297	58.579	44.779	41.583	1.00 52.83
ATOM	2791	CA	PHE	A	297	58.656	45.033	40.160	1.00 53.94
ATOM	2792	CB	PHE	A	297	60.093	45.286	39.730	1.00 55.28

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ATOM	2793	CG	PHE A 297	60.217	45.651	38.293	1.00	57.93
ATOM	2794	CD1	PHE A 297	60.028	46.964	37.884	1.00	57.66
ATOM	2795	CD2	PHE A 297	60.459	44.673	37.334	1.00	59.49
ATOM	2796	CE1	PHE A 297	60.072	47.299	36.539	1.00	59.28
ATOM	2797	CE2	PHE A 297	60.503	44.997	35.990	1.00	59.71
ATOM	2798	CZ	PHE A 297	60.309	46.315	35.590	1.00	59.93
ATOM	2799	C	PHE A 297	58.090	43.837	39.408	1.00	54.31
ATOM	2800	O	PHE A 297	57.245	43.990	38.530	1.00	54.87
ATOM	2801	N	PHE A 298	58.542	42.643	39.776	1.00	55.31
ATOM	2803	CA	PHE A 298	58.058	41.420	39.149	1.00	55.92
ATOM	2804	CB	PHE A 298	58.793	40.199	39.709	1.00	52.95
ATOM	2805	CG	PHE A 298	60.118	39.943	39.057	1.00	49.79
ATOM	2806	CD1	PHE A 298	61.094	40.934	39.019	1.00	46.14
ATOM	2807	CD2	PHE A 298	60.384	38.716	38.463	1.00	47.97
ATOM	2808	CE1	PHE A 298	62.312	40.709	38.400	1.00	44.36
ATOM	2809	CE2	PHE A 298	61.600	38.482	37.842	1.00	46.94
ATOM	2810	CZ	PHE A 298	62.567	39.482	37.810	1.00	45.78
ATOM	2811	C	PHE A 298	56.556	41.274	39.364	1.00	58.12
ATOM	2812	O	PHE A 298	55.904	40.453	38.716	1.00	58.39
ATOM	2813	N	GLY A 299	56.019	42.067	40.287	1.00	60.34
ATOM	2815	CA	GLY A 299	54.599	42.042	40.576	1.00	62.61
ATOM	2816	C	GLY A 299	53.777	42.541	39.404	1.00	64.03
ATOM	2817	O	GLY A 299	52.622	42.156	39.236	1.00	64.07
ATOM	2818	N	THR A 300	54.377	43.379	38.571	1.00	65.39
ATOM	2820	CA	THR A 300	53.672	43.904	37.416	1.00	67.18
ATOM	2821	CB	THR A 300	54.532	44.935	36.658	1.00	66.57
ATOM	2822	OG1	THR A 300	55.806	44.361	36.349	1.00	67.61
ATOM	2824	CG2	THR A 300	54.736	46.181	37.503	1.00	67.44
ATOM	2825	C	THR A 300	53.258	42.785	36.460	1.00	69.21
ATOM	2826	O	THR A 300	52.234	42.896	35.777	1.00	72.16
ATOM	2827	N	PHE A 301	54.055	41.774	36.384	1.00	69.34
ATOM	2829	CA	PHE A 301	53.704	40.675	35.483	1.00	69.26
ATOM	2830	CB	PHE A 301	54.608	40.680	34.241	1.00	66.47
ATOM	2831	CG	PHE A 301	56.070	40.882	34.532	1.00	64.06

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ATOM	2832	CD1	PHE	A	301	56.629	42.154	34.478	1.00 62.60
ATOM	2833	CD2	PHE	A	301	56.895	39.806	34.838	1.00 63.14
ATOM	2834	CE1	PHE	A	301	57.983	42.354	34.716	1.00 61.30
ATOM	2835	CE2	PHE	A	301	58.251	39.995	35.077	1.00 61.28
ATOM	2836	CZ	PHE	A	301	58.795	41.274	35.016	1.00 61.18
ATOM	2837	C	PHE	A	301	53.635	39.268	36.062	1.00 71.49
ATOM	2838	O	PHE	A	301	53.032	38.380	35.458	1.00 71.98
ATOM	2839	N	LEU	A	302	54.199	39.072	37.250	1.00 74.67
ATOM	2841	CA	LEU	A	302	54.198	37.748	37.866	1.00 77.56
ATOM	2842	CB	LEU	A	302	55.573	37.098	37.698	1.00 75.96
ATOM	2843	CG	LEU	A	302	55.833	36.472	36.337	1.00 75.33
ATOM	2844	CD1	LEU	A	302	57.217	35.860	36.332	1.00 75.78
ATOM	2845	CD2	LEU	A	302	54.767	35.425	36.070	1.00 74.63
ATOM	2846	C	LEU	A	302	53.782	37.667	39.338	1.00 80.50
ATOM	2847	O	LEU	A	302	54.567	37.228	40.173	1.00 81.63
ATOM	2848	N	PRO	A	303	52.551	38.075	39.678	1.00 82.47
ATOM	2849	CD	PRO	A	303	51.687	39.012	38.927	1.00 83.87
ATOM	2850	CA	PRO	A	303	52.127	38.002	41.087	1.00 82.85
ATOM	2851	CB	PRO	A	303	51.725	39.440	41.359	1.00 83.29
ATOM	2852	CG	PRO	A	303	50.963	39.803	40.046	1.00 84.24
ATOM	2853	C	PRO	A	303	50.924	37.070	41.346	1.00 82.81
ATOM	2854	O	PRO	A	303	49.809	37.403	40.953	1.00 84.47
ATOM	2855	N	GLU	A	304	51.087	35.893	41.943	1.00 81.68
ATOM	2857	CA	GLU	A	304	52.308	35.254	42.438	1.00 80.61
ATOM	2858	CB	GLU	A	304	52.767	34.203	41.437	1.00 83.61
ATOM	2859	CG	GLU	A	304	51.698	33.132	41.207	1.00 86.52
ATOM	2860	CD	GLU	A	304	51.179	32.502	42.499	1.00 88.36
ATOM	2861	OE1	GLU	A	304	50.103	32.923	42.977	1.00 89.84
ATOM	2862	OE2	GLU	A	304	51.847	31.594	43.036	1.00 89.41
ATOM	2863	C	GLU	A	304	53.501	35.887	43.175	1.00 78.52
ATOM	2864	O	GLU	A	304	53.383	36.142	44.361	1.00 78.12
ATOM	2865	N	VAL	A	305	54.817	36.106	42.616	1.00 76.19
ATOM	2867	CA	VAL	A	305	55.955	36.809	43.226	1.00 74.85

SUBSTITUTE SHEET (RULE 26)

ATOM	2868	CB	VAL	A	305	56.904	37.447	42.170	1.00 74.41
ATOM	2869	CG1	VAL	A	305	57.405	36.392	41.202	1.00 74.39
ATOM	2870	CG2	VAL	A	305	56.218	38.578	41.433	1.00 75.20
ATOM	2871	C	VAL	A	305	55.622	37.833	44.316	1.00 74.68
ATOM	2872	O	VAL	A	305	56.110	37.711	45.438	1.00 75.57
ATOM	2873	N	ALA	A	306	54.746	38.790	44.011	1.00 73.53
ATOM	2875	CA	ALA	A	306	54.357	39.823	44.975	1.00 71.77
ATOM	2876	CB	ALA	A	306	53.893	41.068	44.248	1.00 71.20
ATOM	2877	C	ALA	A	306	53.273	39.348	45.935	1.00 71.50
ATOM	2878	O	ALA	A	306	53.087	39.924	47.005	1.00 70.71
ATOM	2879	N	LYS	A	307	52.563	38.300	45.529	1.00 71.78
ATOM	2881	CA	LYS	A	307	51.474	37.697	46.300	1.00 71.82
ATOM	2882	CB	LYS	A	307	50.508	37.010	45.324	1.00 72.68
ATOM	2883	CG	LYS	A	307	49.332	36.270	45.944	1.00 75.23
ATOM	2884	CD	LYS	A	307	48.473	35.638	44.848	1.00 76.97
ATOM	2885	CE	LYS	A	307	47.247	34.935	45.413	1.00 77.90
ATOM	2886	NZ	LYS	A	307	46.352	34.434	44.331	1.00 77.64
ATOM	2890	C	LYS	A	307	51.946	36.698	47.374	1.00 71.04
ATOM	2891	O	LYS	A	307	51.393	36.651	48.473	1.00 72.05
ATOM	2892	N	LYS	A	308	52.958	35.898	47.050	1.00 69.00
ATOM	2894	CA	LYS	A	308	53.480	34.903	47.979	1.00 66.59
ATOM	2895	CB	LYS	A	308	53.891	33.636	47.219	1.00 70.09
ATOM	2896	CG	LYS	A	308	53.887	32.346	48.046	1.00 75.24
ATOM	2897	CD	LYS	A	308	54.920	32.351	49.172	1.00 79.31
ATOM	2898	CE	LYS	A	308	54.842	31.091	50.027	1.00 81.43
ATOM	2899	NZ	LYS	A	308	55.760	31.141	51.206	1.00 82.05
ATOM	2903	C	LYS	A	308	54.680	35.467	48.722	1.00 64.17
ATOM	2904	O	LYS	A	308	54.840	35.240	49.921	1.00 65.45
ATOM	2905	N	PHE	A	309	55.526	36.200	48.007	1.00 60.99
ATOM	2907	CA	PHE	A	309	56.725	36.784	48.597	1.00 57.85
ATOM	2908	CB	PHE	A	309	57.974	36.274	47.853	1.00 53.07
ATOM	2909	CG	PHE	A	309	58.085	34.762	47.808	1.00 45.45
ATOM	2910	CD1	PHE	A	309	58.551	34.050	48.906	1.00 42.52
ATOM	2911	CD2	PHE	A	309	57.689	34.052	46.679	1.00 43.68

SUBSTITUTE SHEET (RULE 26)

ATOM	2912	CE1	PHE	A	309	58.619	32.655	48.883	1.00	38.70
ATOM	2913	CE2	PHE	A	309	57.754	32.655	46.647	1.00	42.05
ATOM	2914	CZ	PHE	A	309	58.219	31.959	47.753	1.00	39.93
ATOM	2915	C	PHE	A	309	56.616	38.312	48.553	1.00	58.92
ATOM	2916	O	PHE	A	309	57.266	38.978	47.743	1.00	58.89
ATOM	2917	N	PRO	A	310	55.822	38.885	49.472	1.00	60.26
ATOM	2918	CD	PRO	A	310	55.173	38.142	50.569	1.00	61.34
ATOM	2919	CA	PRO	A	310	55.560	40.320	49.613	1.00	61.10
ATOM	2920	CB	PRO	A	310	54.522	40.358	50.736	1.00	62.64
ATOM	2921	CG	PRO	A	310	54.934	39.217	51.598	1.00	61.52
ATOM	2922	C	PRO	A	310	56.737	41.239	49.927	1.00	61.05
ATOM	2923	O	PRO	A	310	57.307	41.187	51.016	1.00	61.70
ATOM	2924	N	ASN	A	311	57.044	42.121	48.979	1.00	62.21
ATOM	2926	CA	ASN	A	311	58.116	43.111	49.111	1.00	63.11
ATOM	2927	CB	ASN	A	311	57.667	44.247	50.037	1.00	66.59
ATOM	2928	CG	ASN	A	311	58.589	45.448	49.976	1.00	69.63
ATOM	2929	OD1	ASN	A	311	58.596	46.186	48.991	1.00	71.72
ATOM	2930	ND2	ASN	A	311	59.373	45.651	51.027	1.00	71.51
ATOM	2933	C	ASN	A	311	59.458	42.547	49.583	1.00	61.81
ATOM	2934	O	ASN	A	311	59.855	42.737	50.738	1.00	63.25
ATOM	2935	N	MET	A	312	60.155	41.870	48.673	1.00	58.63
ATOM	2937	CA	MET	A	312	61.459	41.266	48.950	1.00	53.64
ATOM	2938	CB	MET	A	312	61.316	39.768	49.269	1.00	53.53
ATOM	2939	CG	MET	A	312	60.599	39.405	50.570	1.00	52.28
ATOM	2940	SD	MET	A	312	60.259	37.617	50.633	1.00	52.18
ATOM	2941	CE	MET	A	312	58.896	37.534	51.788	1.00	54.70
ATOM	2942	C	MET	A	312	62.320	41.411	47.699	1.00	49.72
ATOM	2943	O	MET	A	312	61.801	41.656	46.605	1.00	49.26
ATOM	2944	N	LYS	A	313	63.630	41.275	47.865	1.00	44.80
ATOM	2946	CA	LYS	A	313	64.549	41.363	46.741	1.00	41.81
ATOM	2947	CB	LYS	A	313	65.952	41.707	47.230	1.00	42.38
ATOM	2948	CG	LYS	A	313	66.050	43.081	47.846	1.00	47.04
ATOM	2949	CD	LYS	A	313	65.762	44.159	46.818	1.00	49.35

SUBSTITUTE SHEET (RULE 26)

ATOM	2950	CE	LYS	A	313	65.599	45.515	47.481	1.00 53.10
ATOM	2951	NZ	LYS	A	313	66.805	45.897	48.268	1.00 56.75
ATOM	2955	C	LYS	A	313	64.562	40.018	46.026	1.00 39.61
ATOM	2956	O	LYS	A	313	64.133	39.013	46.592	1.00 38.93
ATOM	2957	N	ILE	A	314	65.040	40.005	44.786	1.00 37.30
ATOM	2959	CA	ILE	A	314	65.115	38.785	43.995	1.00 34.17
ATOM	2960	CB	ILE	A	314	64.224	38.865	42.716	1.00 33.93
ATOM	2961	CG2	ILE	A	314	64.607	37.783	41.708	1.00 32.86
ATOM	2962	CG1	ILE	A	314	62.745	38.728	43.093	1.00 33.03
ATOM	2963	CD1	ILE	A	314	61.824	38.459	41.920	1.00 32.90
ATOM	2964	C	ILE	A	314	66.567	38.565	43.604	1.00 33.46
ATOM	2965	O	ILE	A	314	67.272	39.512	43.271	1.00 32.77
ATOM	2966	N	GLN	A	315	67.024	37.321	43.698	1.00 32.44
ATOM	2968	CA	GLN	A	315	68.391	36.975	43.336	1.00 32.66
ATOM	2969	CB	GLN	A	315	69.118	36.366	44.529	1.00 34.35
ATOM	2970	CG	GLN	A	315	70.624	36.305	44.376	1.00 35.08
ATOM	2971	CD	GLN	A	315	71.317	35.839	45.639	1.00 33.95
ATOM	2972	OE1	GLN	A	315	71.579	36.620	46.548	1.00 34.44
ATOM	2973	NE2	GLN	A	315	71.607	34.554	45.701	1.00 37.53
ATOM	2976	C	GLN	A	315	68.307	35.964	42.207	1.00 33.04
ATOM	2977	O	GLN	A	315	67.520	35.024	42.271	1.00 35.05
ATOM	2978	N	ILE	A	316	69.116	36.155	41.175	1.00 34.76
ATOM	2980	CA	ILE	A	316	69.106	35.268	40.018	1.00 33.81
ATOM	2981	CB	ILE	A	316	68.711	36.067	38.750	1.00 35.72
ATOM	2982	CG2	ILE	A	316	68.944	35.247	37.498	1.00 37.16
ATOM	2983	CG1	ILE	A	316	67.249	36.518	38.864	1.00 36.98
ATOM	2984	CD1	ILE	A	316	66.695	37.179	37.633	1.00 38.34
ATOM	2985	C	ILE	A	316	70.445	34.548	39.823	1.00 32.92
ATOM	2986	O	ILE	A	316	71.513	35.160	39.900	1.00 33.03
ATOM	2987	N	HIS	A	317	70.386	33.238	39.609	1.00 33.55
ATOM	2989	CA	HIS	A	317	71.586	32.428	39.409	1.00 32.00
ATOM	2990	CB	HIS	A	317	71.532	31.162	40.264	1.00 32.50
ATOM	2991	CG	HIS	A	317	71.659	31.411	41.735	1.00 32.14
ATOM	2992	CD2	HIS	A	317	71.889	32.548	42.435	1.00 31.63

SUBSTITUTE SHEET (RULE 26)

ATOM	2993	ND1	HIS	A	317	71.572	30.398	42.666	1.00 32.81
ATOM	2995	CE1	HIS	A	317	71.746	30.899	43.875	1.00 33.94
ATOM	2996	NE2	HIS	A	317	71.941	32.201	43.761	1.00 32.58
ATOM	2998	C	HIS	A	317	71.720	32.014	37.953	1.00 33.04
ATOM	2999	O	HIS	A	317	70.844	31.335	37.416	1.00 33.39
ATOM	3000	N	VAL	A	318	72.842	32.377	37.344	1.00 33.42
ATOM	3002	CA	VAL	A	318	73.129	32.059	35.952	1.00 31.61
ATOM	3003	CB	VAL	A	318	73.535	33.338	35.193	1.00 29.43
ATOM	3004	CG1	VAL	A	318	73.993	33.003	33.789	1.00 30.90
ATOM	3005	CG2	VAL	A	318	72.376	34.311	35.161	1.00 27.51
ATOM	3006	C	VAL	A	318	74.273	31.043	35.861	1.00 32.81
ATOM	3007	O	VAL	A	318	75.392	31.325	36.296	1.00 33.30
ATOM	3008	N	SER	A	319	73.990	29.858	35.329	1.00 32.14
ATOM	3010	CA	SER	A	319	75.021	28.836	35.175	1.00 32.12
ATOM	3011	CB	SER	A	319	74.919	27.778	36.271	1.00 28.41
ATOM	3012	OG	SER	A	319	73.723	27.039	36.158	1.00 29.90
ATOM	3014	C	SER	A	319	74.900	28.170	33.815	1.00 33.52
ATOM	3015	O	SER	A	319	73.834	28.174	33.210	1.00 37.50
ATOM	3016	N	ALA	A	320	76.005	27.632	33.319	1.00 35.33
ATOM	3018	CA	ALA	A	320	76.009	26.958	32.031	1.00 35.02
ATOM	3019	CB	ALA	A	320	77.417	26.914	31.461	1.00 36.41
ATOM	3020	C	ALA	A	320	75.466	25.547	32.210	1.00 36.23
ATOM	3021	O	ALA	A	320	75.955	24.786	33.047	1.00 35.14
ATOM	3022	N	SER	A	321	74.459	25.204	31.415	1.00 38.15
ATOM	3024	CA	SER	A	321	73.835	23.891	31.478	1.00 38.99
ATOM	3025	CB	SER	A	321	72.472	23.935	30.786	1.00 38.78
ATOM	3026	OG	SER	A	321	72.418	24.984	29.834	1.00 40.20
ATOM	3028	C	SER	A	321	74.724	22.824	30.848	1.00 40.78
ATOM	3029	O	SER	A	321	74.942	21.760	31.430	1.00 44.24
ATOM	3030	N	THR	A	322	75.249	23.126	29.666	1.00 39.66
ATOM	3032	CA	THR	A	322	76.119	22.214	28.939	1.00 36.30
ATOM	3033	CB	THR	A	322	75.355	21.553	27.750	1.00 39.80
ATOM	3034	OG1	THR	A	322	74.613	22.548	27.027	1.00 40.24

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ATOM	3036	CG2	THR	A	322	74.398	20.473	28.253	1.00 41.99
ATOM	3037	C	THR	A	322	77.332	22.985	28.416	1.00 33.41
ATOM	3038	O	THR	A	322	77.372	24.214	28.487	1.00 31.80
ATOM	3039	N	PRO	A	323	78.378	22.272	27.966	1.00 32.97
ATOM	3040	CD	PRO	A	323	78.606	20.826	28.133	1.00 31.42
ATOM	3041	CA	PRO	A	323	79.581	22.925	27.439	1.00 31.79
ATOM	3042	CB	PRO	A	323	80.471	21.739	27.089	1.00 31.21
ATOM	3043	CG	PRO	A	323	80.099	20.740	28.128	1.00 31.27
ATOM	3044	C	PRO	A	323	79.279	23.757	26.191	1.00 33.72
ATOM	3045	O	PRO	A	323	78.727	23.237	25.218	1.00 35.68
ATOM	3046	N	PRO	A	324	79.650	25.053	26.196	1.00 34.41
ATOM	3047	CD	PRO	A	324	80.303	25.799	27.286	1.00 34.36
ATOM	3048	CA	PRO	A	324	79.407	25.933	25.050	1.00 36.18
ATOM	3049	CB	PRO	A	324	79.863	27.301	25.567	1.00 34.56
ATOM	3050	CG	PRO	A	324	80.913	26.963	26.551	1.00 34.54
ATOM	3051	C	PRO	A	324	80.186	25.511	23.811	1.00 39.38
ATOM	3052	O	PRO	A	324	81.397	25.278	23.871	1.00 43.04
ATOM	3053	N	HIS	A	325	79.468	25.364	22.704	1.00 39.27
ATOM	3055	CA	HIS	A	325	80.064	24.973	21.434	1.00 39.40
ATOM	3056	CB	HIS	A	325	79.045	24.236	20.562	1.00 44.72
ATOM	3057	CG	HIS	A	325	78.817	22.813	20.955	1.00 49.32
ATOM	3058	CD2	HIS	A	325	79.471	22.015	21.831	1.00 51.91
ATOM	3059	ND1	HIS	A	325	77.817	22.041	20.405	1.00 52.21
ATOM	3061	CE1	HIS	A	325	77.864	20.827	20.924	1.00 53.83
ATOM	3062	NE2	HIS	A	325	78.859	20.785	21.793	1.00 54.25
ATOM	3064	C	HIS	A	325	80.537	26.183	20.658	1.00 37.89
ATOM	3065	O	HIS	A	325	80.011	27.285	20.825	1.00 39.24
ATOM	3066	N	LEU	A	326	81.514	25.958	19.788	1.00 36.12
ATOM	3068	CA	LEU	A	326	82.056	26.993	18.928	1.00 34.45
ATOM	3069	CB	LEU	A	326	83.370	27.535	19.487	1.00 34.16
ATOM	3070	CG	LEU	A	326	83.906	28.758	18.745	1.00 34.49
ATOM	3071	CD1	LEU	A	326	82.912	29.878	18.854	1.00 36.18
ATOM	3072	CD2	LEU	A	326	85.220	29.194	19.321	1.00 38.20
ATOM	3073	C	LEU	A	326	82.285	26.329	17.569	1.00 34.87

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ATOM	3074	O	LEU	A	326	82.981	25.311	17.469	1.00 35.31
ATOM	3075	N	SER	A	327	81.639	26.863	16.542	1.00 32.90
ATOM	3077	CA	SER	A	327	81.755	26.323	15.202	1.00 32.76
ATOM	3078	CB	SER	A	327	80.359	26.173	14.591	1.00 34.44
ATOM	3079	OG	SER	A	327	80.390	25.407	13.394	1.00 41.05
ATOM	3081	C	SER	A	327	82.607	27.247	14.343	1.00 30.57
ATOM	3082	O	SER	A	327	82.391	28.458	14.329	1.00 31.41
ATOM	3083	N	VAL	A	328	83.601	26.691	13.658	1.00 29.84
ATOM	3085	CA	VAL	A	328	84.452	27.502	12.795	1.00 28.60
ATOM	3086	CB	VAL	A	328	85.951	27.275	13.056	1.00 25.61
ATOM	3087	CG1	VAL	A	328	86.733	28.389	12.423	1.00 24.98
ATOM	3088	CG2	VAL	A	328	86.245	27.218	14.544	1.00 23.23
ATOM	3089	C	VAL	A	328	84.159	27.174	11.336	1.00 30.19
ATOM	3090	O	VAL	A	328	84.221	26.015	10.928	1.00 29.56
ATOM	3091	N	GLN	A	329	83.791	28.194	10.569	1.00 32.32
ATOM	3093	CA	GLN	A	329	83.479	28.038	9.150	1.00 34.28
ATOM	3094	CB	GLN	A	329	81.956	27.972	8.939	1.00 39.33
ATOM	3095	CG	GLN	A	329	81.222	26.924	9.774	1.00 48.55
ATOM	3096	CD	GLN	A	329	80.246	27.532	10.785	1.00 53.31
ATOM	3097	OE1	GLN	A	329	79.321	26.860	11.245	1.00 57.70
ATOM	3098	NE2	GLN	A	329	80.456	28.796	11.142	1.00 53.89
ATOM	3101	C	GLN	A	329	84.050	29.259	8.416	1.00 32.74
ATOM	3102	O	GLN	A	329	84.337	30.279	9.048	1.00 34.32
ATOM	3103	N	PRO	A	330	84.176	29.193	7.073	1.00 30.85
ATOM	3104	CD	PRO	A	330	83.896	28.019	6.226	1.00 27.63
ATOM	3105	CA	PRO	A	330	84.711	30.301	6.265	1.00 30.72
ATOM	3106	CB	PRO	A	330	84.597	29.765	4.842	1.00 27.09
ATOM	3107	CG	PRO	A	330	84.754	28.286	5.026	1.00 27.10
ATOM	3108	C	PRO	A	330	83.968	31.635	6.416	1.00 33.05
ATOM	3109	O	PRO	A	330	84.501	32.695	6.084	1.00 34.38
ATOM	3110	N	THR	A	331	82.733	31.575	6.904	1.00 36.91
ATOM	3112	CA	THR	A	331	81.918	32.767	7.106	1.00 39.55
ATOM	3113	CB	THR	A	331	80.414	32.414	7.065	1.00 41.23

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ATOM	3114	OG1	THR	A	331	80.179	31.221	7.826	1.00 42.58
ATOM	3116	CG2	THR	A	331	79.959	32.180	5.630	1.00 42.18
ATOM	3117	C	THR	A	331	82.244	33.469	8.425	1.00 41.21
ATOM	3118	O	THR	A	331	82.114	34.691	8.535	1.00 44.22
ATOM	3119	N	GLY	A	332	82.671	32.691	9.418	1.00 39.90
ATOM	3121	CA	GLY	A	332	83.005	33.240	10.720	1.00 36.14
ATOM	3122	C	GLY	A	332	82.788	32.188	11.788	1.00 36.29
ATOM	3123	O	GLY	A	332	82.399	31.058	11.472	1.00 36.21
ATOM	3124	N	LEU	A	333	83.048	32.542	13.044	1.00 35.70
ATOM	3126	CA	LEU	A	333	82.875	31.606	14.153	1.00 34.12
ATOM	3127	CB	LEU	A	333	84.037	31.704	15.157	1.00 31.15
ATOM	3128	CG	LEU	A	333	85.438	32.183	14.766	1.00 30.79
ATOM	3129	CD1	LEU	A	333	86.402	31.841	15.886	1.00 29.93
ATOM	3130	CD2	LEU	A	333	85.908	31.539	13.492	1.00 32.11
ATOM	3131	C	LEU	A	333	81.570	31.889	14.889	1.00 34.02
ATOM	3132	O	LEU	A	333	81.283	33.037	15.233	1.00 35.28
ATOM	3133	N	THR	A	334	80.777	30.850	15.123	1.00 32.89
ATOM	3135	CA	THR	A	334	79.521	30.997	15.842	1.00 30.97
ATOM	3136	CB	THR	A	334	78.344	30.435	15.037	1.00 30.40
ATOM	3137	OG1	THR	A	334	78.673	29.124	14.568	1.00 36.09
ATOM	3139	CG2	THR	A	334	78.043	31.324	13.850	1.00 27.87
ATOM	3140	C	THR	A	334	79.649	30.274	17.184	1.00 30.59
ATOM	3141	O	THR	A	334	80.293	29.229	17.267	1.00 31.11
ATOM	3142	N	PHE	A	335	79.052	30.853	18.225	1.00 31.55
ATOM	3144	CA	PHE	A	335	79.095	30.334	19.598	1.00 30.95
ATOM	3145	CB	PHE	A	335	79.579	31.465	20.530	1.00 31.73
ATOM	3146	CG	PHE	A	335	80.138	31.001	21.853	1.00 32.43
ATOM	3147	CD1	PHE	A	335	81.224	30.134	21.907	1.00 34.10
ATOM	3148	CD2	PHE	A	335	79.611	31.483	23.044	1.00 33.32
ATOM	3149	CE1	PHE	A	335	81.779	29.755	23.124	1.00 36.27
ATOM	3150	CE2	PHE	A	335	80.156	31.113	24.267	1.00 36.93
ATOM	3151	CZ	PHE	A	335	81.243	30.248	24.308	1.00 36.83
ATOM	3152	C	PHE	A	335	77.674	29.910	19.975	1.00 29.88
ATOM	3153	O	PHE	A	335	76.722	30.616	19.666	1.00 29.27

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ATOM	3154	N	TYR	A	336	77.533	28.779	20.658	1.00 30.87
ATOM	3156	CA	TYR	A	336	76.216	28.281	21.052	1.00 33.87
ATOM	3157	CB	TYR	A	336	75.936	26.953	20.345	1.00 35.86
ATOM	3158	CG	TYR	A	336	76.081	27.036	18.844	1.00 36.58
ATOM	3159	CD1	TYR	A	336	75.107	27.665	18.072	1.00 38.45
ATOM	3160	CE1	TYR	A	336	75.245	27.791	16.700	1.00 38.32
ATOM	3161	CD2	TYR	A	336	77.207	26.526	18.198	1.00 34.97
ATOM	3162	CE2	TYR	A	336	77.357	26.647	16.819	1.00 36.42
ATOM	3163	CZ	TYR	A	336	76.369	27.285	16.078	1.00 37.51
ATOM	3164	OH	TYR	A	336	76.494	27.435	14.715	1.00 41.83
ATOM	3166	C	TYR	A	336	76.104	28.096	22.565	1.00 36.66
ATOM	3167	O	TYR	A	336	76.280	26.988	23.074	1.00 39.11
ATOM	3168	N	PRO	A	337	75.858	29.187	23.309	1.00 36.71
ATOM	3169	CD	PRO	A	337	75.890	30.605	22.904	1.00 36.11
ATOM	3170	CA	PRO	A	337	75.740	29.069	24.761	1.00 35.26
ATOM	3171	CB	PRO	A	337	76.156	30.449	25.234	1.00 35.76
ATOM	3172	CG	PRO	A	337	75.564	31.327	24.192	1.00 36.30
ATOM	3173	C	PRO	A	337	74.325	28.751	25.198	1.00 36.60
ATOM	3174	O	PRO	A	337	73.358	29.231	24.604	1.00 39.83
ATOM	3175	N	ALA	A	338	74.218	27.909	26.218	1.00 36.08
ATOM	3177	CA	ALA	A	338	72.944	27.512	26.802	1.00 35.56
ATOM	3178	CB	ALA	A	338	72.671	26.039	26.533	1.00 36.41
ATOM	3179	C	ALA	A	338	73.116	27.752	28.294	1.00 36.55
ATOM	3180	O	ALA	A	338	74.059	27.241	28.902	1.00 37.65
ATOM	3181	N	VAL	A	339	72.256	28.576	28.878	1.00 36.13
ATOM	3183	CA	VAL	A	339	72.360	28.872	30.295	1.00 34.95
ATOM	3184	CB	VAL	A	339	72.771	30.346	30.538	1.00 33.81
ATOM	3185	CG1	VAL	A	339	74.046	30.667	29.776	1.00 36.08
ATOM	3186	CG2	VAL	A	339	71.658	31.293	30.139	1.00 33.93
ATOM	3187	C	VAL	A	339	71.071	28.578	31.043	1.00 35.50
ATOM	3188	O	VAL	A	339	69.990	28.553	30.451	1.00 38.45
ATOM	3189	N	ASP	A	340	71.208	28.295	32.335	1.00 33.66
ATOM	3191	CA	ASP	A	340	70.078	28.029	33.213	1.00 31.12

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ATOM	3192	CB	ASP	A	340	70.318	26.785	34.067	1.00 31.54
ATOM	3193	CG	ASP	A	340	69.813	25.520	33.411	1.00 33.33
ATOM	3194	OD1	ASP	A	340	68.895	25.606	32.569	1.00 35.59
ATOM	3195	OD2	ASP	A	340	70.324	24.432	33.742	1.00 35.60
ATOM	3196	C	ASP	A	340	70.003	29.235	34.108	1.00 29.12
ATOM	3197	O	ASP	A	340	70.968	29.555	34.794	1.00 29.84
ATOM	3198	N	VAL	A	341	68.890	29.948	34.040	1.00 28.41
ATOM	3200	CA	VAL	A	341	68.687	31.133	34.846	1.00 28.82
ATOM	3201	CB	VAL	A	341	68.249	32.316	33.969	1.00 29.73
ATOM	3202	CG1	VAL	A	341	67.868	33.496	34.831	1.00 27.89
ATOM	3203	CG2	VAL	A	341	69.364	32.703	33.017	1.00 28.62
ATOM	3204	C	VAL	A	341	67.592	30.833	35.852	1.00 30.90
ATOM	3205	O	VAL	A	341	66.456	30.596	35.459	1.00 34.21
ATOM	3206	N	GLN	A	342	67.931	30.821	37.139	1.00 31.91
ATOM	3208	CA	GLN	A	342	66.948	30.546	38.191	1.00 31.19
ATOM	3209	CB	GLN	A	342	67.375	29.345	39.039	1.00 31.37
ATOM	3210	CG	GLN	A	342	66.319	28.867	40.028	1.00 31.56
ATOM	3211	CD	GLN	A	342	66.706	27.570	40.706	1.00 33.87
ATOM	3212	OE1	GLN	A	342	67.841	27.111	40.590	1.00 37.83
ATOM	3213	NE2	GLN	A	342	65.770	26.979	41.431	1.00 35.30
ATOM	3216	C	GLN	A	342	66.752	31.761	39.088	1.00 31.20
ATOM	3217	O	GLN	A	342	67.724	32.374	39.537	1.00 31.67
ATOM	3218	N	ALA	A	343	65.494	32.114	39.327	1.00 30.96
ATOM	3220	CA	ALA	A	343	65.169	33.254	40.169	1.00 28.72
ATOM	3221	CB	ALA	A	343	64.042	34.054	39.563	1.00 28.77
ATOM	3222	C	ALA	A	343	64.782	32.778	41.552	1.00 28.72
ATOM	3223	O	ALA	A	343	64.011	31.826	41.700	1.00 30.49
ATOM	3224	N	PHE	A	344	65.320	33.447	42.559	1.00 26.88
ATOM	3226	CA	PHE	A	344	65.040	33.125	43.945	1.00 26.71
ATOM	3227	CB	PHE	A	344	66.316	32.718	44.673	1.00 21.35
ATOM	3228	CG	PHE	A	344	66.891	31.428	44.210	1.00 19.20
ATOM	3229	CD1	PHE	A	344	67.806	31.396	43.173	1.00 20.33
ATOM	3230	CD2	PHE	A	344	66.547	30.247	44.834	1.00 15.57
ATOM	3231	CE1	PHE	A	344	68.372	30.198	42.766	1.00 19.57

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ATOM	3232	CE2	PHE	A	344	67.106	29.049	44.438	1.00 17.79
ATOM	3233	CZ	PHE	A	344	68.023	29.026	43.401	1.00 19.23
ATOM	3234	C	PHE	A	344	64.523	34.382	44.608	1.00 29.77
ATOM	3235	O	PHE	A	344	64.847	35.495	44.189	1.00 33.20
ATOM	3236	N	ALA	A	345	63.712	34.206	45.637	1.00 29.97
ATOM	3238	CA	ALA	A	345	63.204	35.331	46.390	1.00 30.90
ATOM	3239	CB	ALA	A	345	61.720	35.147	46.685	1.00 32.55
ATOM	3240	C	ALA	A	345	64.030	35.266	47.669	1.00 31.52
ATOM	3241	O	ALA	A	345	64.230	34.186	48.220	1.00 32.91
ATOM	3242	N	VAL	A	346	64.588	36.395	48.082	1.00 32.21
ATOM	3244	CA	VAL	A	346	65.403	36.449	49.287	1.00 33.87
ATOM	3245	CB	VAL	A	346	66.490	37.559	49.176	1.00 34.53
ATOM	3246	CG1	VAL	A	346	67.430	37.537	50.383	1.00 32.13
ATOM	3247	CG2	VAL	A	346	67.276	37.394	47.892	1.00 33.38
ATOM	3248	C	VAL	A	346	64.497	36.755	50.474	1.00 36.21
ATOM	3249	O	VAL	A	346	63.985	37.871	50.597	1.00 38.00
ATOM	3250	N	LEU	A	347	64.278	35.759	51.327	1.00 37.36
ATOM	3252	CA	LEU	A	347	63.445	35.928	52.516	1.00 39.35
ATOM	3253	CB	LEU	A	347	63.172	34.567	53.162	1.00 37.87
ATOM	3254	CG	LEU	A	347	62.664	33.460	52.238	1.00 37.83
ATOM	3255	CD1	LEU	A	347	62.315	32.231	53.057	1.00 36.57
ATOM	3256	CD2	LEU	A	347	61.461	33.945	51.462	1.00 39.01
ATOM	3257	C	LEU	A	347	64.157	36.847	53.519	1.00 42.26
ATOM	3258	O	LEU	A	347	65.376	37.021	53.449	1.00 44.26
ATOM	3259	N	PRO	A	348	63.418	37.410	54.495	1.00 43.97
ATOM	3260	CD	PRO	A	348	61.973	37.254	54.728	1.00 43.89
ATOM	3261	CA	PRO	A	348	64.002	38.309	55.505	1.00 43.61
ATOM	3262	CB	PRO	A	348	62.796	38.689	56.364	1.00 44.62
ATOM	3263	CG	PRO	A	348	61.875	37.514	56.206	1.00 44.98
ATOM	3264	C	PRO	A	348	65.138	37.751	56.364	1.00 42.78
ATOM	3265	O	PRO	A	348	65.685	38.471	57.195	1.00 43.70
ATOM	3266	N	ASN	A	349	65.478	36.478	56.184	1.00 42.71
ATOM	3268	CA	ASN	A	349	66.556	35.849	56.947	1.00 41.55

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ATOM	3269	CB	ASN A 349	66.046	34.591	57.659	1.00	41.16
ATOM	3270	CG	ASN A 349	65.583	33.518	56.689	1.00	43.53
ATOM	3271	OD1	ASN A 349	65.524	33.748	55.479	1.00	44.53
ATOM	3272	ND2	ASN A 349	65.256	32.339	57.210	1.00	43.58
ATOM	3275	C	ASN A 349	67.731	35.482	56.038	1.00	41.09
ATOM	3276	O	ASN A 349	68.662	34.801	56.469	1.00	41.04
ATOM	3277	N	SER A 350	67.678	35.954	54.793	1.00	40.23
ATOM	3279	CA	SER A 350	68.697	35.704	53.768	1.00	39.62
ATOM	3280	CB	SER A 350	70.122	35.854	54.314	1.00	40.62
ATOM	3281	OG	SER A 350	70.518	37.214	54.317	1.00	46.79
ATOM	3283	C	SER A 350	68.561	34.364	53.067	1.00	37.74
ATOM	3284	O	SER A 350	69.339	34.063	52.168	1.00	40.17
ATOM	3285	N	ALA A 351	67.581	33.562	53.471	1.00	34.00
ATOM	3287	CA	ALA A 351	67.373	32.266	52.846	1.00	31.70
ATOM	3288	CB	ALA A 351	66.426	31.429	53.670	1.00	31.56
ATOM	3289	C	ALA A 351	66.799	32.505	51.455	1.00	32.27
ATOM	3290	O	ALA A 351	66.150	33.526	51.212	1.00	34.50
ATOM	3291	N	LEU A 352	67.022	31.560	50.549	1.00	30.81
ATOM	3293	CA	LEU A 352	66.541	31.681	49.179	1.00	27.71
ATOM	3294	CB	LEU A 352	67.678	31.358	48.203	1.00	22.61
ATOM	3295	CG	LEU A 352	69.026	32.057	48.373	1.00	14.74
ATOM	3296	CD1	LEU A 352	69.958	31.612	47.280	1.00	13.29
ATOM	3297	CD2	LEU A 352	68.853	33.554	48.306	1.00	14.68
ATOM	3298	C	LEU A 352	65.348	30.775	48.886	1.00	29.37
ATOM	3299	O	LEU A 352	65.375	29.573	49.179	1.00	30.14
ATOM	3300	N	ALA A 353	64.309	31.349	48.289	1.00	31.25
ATOM	3302	CA	ALA A 353	63.110	30.592	47.929	1.00	34.26
ATOM	3303	CB	ALA A 353	61.882	31.226	48.554	1.00	35.51
ATOM	3304	C	ALA A 353	62.982	30.555	46.403	1.00	36.03
ATOM	3305	O	ALA A 353	62.793	31.587	45.764	1.00	37.52
ATOM	3306	N	SER A 354	63.110	29.362	45.832	1.00	37.41
ATOM	3308	CA	SER A 354	63.054	29.162	44.388	1.00	37.85
ATOM	3309	CB	SER A 354	63.338	27.687	44.070	1.00	40.08
ATOM	3310	OG	SER A 354	63.380	27.434	42.673	1.00	45.78

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ATOM	3312	C	SER	A	354	61.744	29.601	43.741	1.00 37.70
ATOM	3313	O	SER	A	354	60.684	29.060	44.043	1.00 40.21
ATOM	3314	N	LEU	A	355	61.830	30.572	42.840	1.00 36.34
ATOM	3316	CA	LEU	A	355	60.657	31.074	42.137	1.00 35.04
ATOM	3317	CB	LEU	A	355	60.839	32.553	41.782	1.00 30.99
ATOM	3318	CG	LEU	A	355	60.830	33.547	42.939	1.00 28.58
ATOM	3319	CD1	LEU	A	355	61.028	34.955	42.423	1.00 28.81
ATOM	3320	CD2	LEU	A	355	59.520	33.441	43.678	1.00 30.20
ATOM	3321	C	LEU	A	355	60.399	30.255	40.868	1.00 36.96
ATOM	3322	O	LEU	A	355	59.363	29.592	40.745	1.00 36.42
ATOM	3323	N	PHE	A	356	61.356	30.286	39.939	1.00 37.24
ATOM	3325	CA	PHE	A	356	61.251	29.556	38.673	1.00 36.22
ATOM	3326	CB	PHE	A	356	60.315	30.291	37.699	1.00 33.82
ATOM	3327	CG	PHE	A	356	60.661	31.741	37.491	1.00 30.90
ATOM	3328	CD1	PHE	A	356	61.786	32.110	36.768	1.00 29.04
ATOM	3329	CD2	PHE	A	356	59.859	32.739	38.027	1.00 30.48
ATOM	3330	CE1	PHE	A	356	62.111	33.451	36.586	1.00 28.29
ATOM	3331	CE2	PHE	A	356	60.179	34.081	37.848	1.00 30.44
ATOM	3332	CZ	PHE	A	356	61.308	34.435	37.128	1.00 25.36
ATOM	3333	C	PHE	A	356	62.611	29.356	38.011	1.00 36.47
ATOM	3334	O	PHE	A	356	63.546	30.112	38.271	1.00 39.86
ATOM	3335	N	LEU	A	357	62.707	28.345	37.151	1.00 36.72
ATOM	3337	CA	LEU	A	357	63.937	28.035	36.423	1.00 35.97
ATOM	3338	CB	LEU	A	357	64.358	26.585	36.670	1.00 34.25
ATOM	3339	CG	LEU	A	357	65.593	26.104	35.904	1.00 32.69
ATOM	3340	CD1	LEU	A	357	66.828	26.854	36.354	1.00 30.30
ATOM	3341	CD2	LEU	A	357	65.784	24.620	36.120	1.00 34.02
ATOM	3342	C	LEU	A	357	63.721	28.252	34.925	1.00 36.64
ATOM	3343	O	LEU	A	357	62.805	27.678	34.333	1.00 39.03
ATOM	3344	N	ILE	A	358	64.585	29.054	34.318	1.00 35.88
ATOM	3346	CA	ILE	A	358	64.508	29.367	32.899	1.00 34.57
ATOM	3347	CB	ILE	A	358	64.510	30.903	32.672	1.00 33.20
ATOM	3348	CG2	ILE	A	358	64.653	31.239	31.208	1.00 31.65

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ATOM	3349	CG1	ILE	A	358	63.220	31.510	33.207	1.00 33.82
ATOM	3350	CD1	ILE	A	358	61.978	30.907	32.602	1.00 34.80
ATOM	3351	C	ILE	A	358	65.677	28.748	32.143	1.00 36.24
ATOM	3352	O	ILE	A	358	66.784	28.628	32.666	1.00 36.67
ATOM	3353	N	GLY	A	359	65.405	28.338	30.912	1.00 38.02
ATOM	3355	CA	GLY	A	359	66.419	27.753	30.061	1.00 37.56
ATOM	3356	C	GLY	A	359	66.597	28.704	28.902	1.00 38.10
ATOM	3357	O	GLY	A	359	65.679	28.932	28.113	1.00 38.54
ATOM	3358	N	MET	A	360	67.769	29.305	28.830	1.00 37.31
ATOM	3360	CA	MET	A	360	68.060	30.252	27.785	1.00 36.92
ATOM	3361	CB	MET	A	360	68.515	31.560	28.405	1.00 38.52
ATOM	3362	CG	MET	A	360	68.813	32.656	27.421	1.00 42.50
ATOM	3363	SD	MET	A	360	69.679	33.987	28.246	1.00 49.37
ATOM	3364	CE	MET	A	360	68.747	34.125	29.725	1.00 46.11
ATOM	3365	C	MET	A	360	69.154	29.686	26.907	1.00 38.15
ATOM	3366	O	MET	A	360	69.986	28.899	27.347	1.00 38.64
ATOM	3367	N	HIS	A	361	69.114	30.054	25.641	1.00 39.81
ATOM	3369	CA	HIS	A	361	70.095	29.612	24.667	1.00 41.81
ATOM	3370	CB	HIS	A	361	69.766	28.215	24.131	1.00 45.81
ATOM	3371	CG	HIS	A	361	68.310	27.988	23.878	1.00 51.49
ATOM	3372	CD2	HIS	A	361	67.290	27.716	24.728	1.00 54.71
ATOM	3373	ND1	HIS	A	361	67.753	28.041	22.618	1.00 53.69
ATOM	3375	CE1	HIS	A	361	66.455	27.813	22.702	1.00 55.98
ATOM	3376	NE2	HIS	A	361	66.148	27.614	23.972	1.00 57.77
ATOM	3378	C	HIS	A	361	70.032	30.642	23.569	1.00 41.72
ATOM	3379	O	HIS	A	361	69.003	31.295	23.387	1.00 42.60
ATOM	3380	N	THR	A	362	71.132	30.816	22.858	1.00 40.54
ATOM	3382	CA	THR	A	362	71.168	31.803	21.803	1.00 38.28
ATOM	3383	CB	THR	A	362	71.452	33.206	22.399	1.00 38.27
ATOM	3384	OG1	THR	A	362	71.408	34.200	21.371	1.00 40.01
ATOM	3386	CG2	THR	A	362	72.799	33.241	23.082	1.00 38.36
ATOM	3387	C	THR	A	362	72.244	31.391	20.818	1.00 37.84
ATOM	3388	O	THR	A	362	72.692	30.245	20.829	1.00 38.47
ATOM	3389	N	THR	A	363	72.620	32.315	19.948	1.00 37.83

SUBSTITUTE SHEET (RULE 26)

ATOM	3391	CA	THR	A	363	73.640	32.091	18.940	1.00 38.05
ATOM	3392	CB	THR	A	363	73.007	31.617	17.603	1.00 38.92
ATOM	3393	OG1	THR	A	363	73.993	31.618	16.567	1.00 41.55
ATOM	3395	CG2	THR	A	363	71.855	32.515	17.193	1.00 42.85
ATOM	3396	C	THR	A	363	74.333	33.436	18.773	1.00 36.99
ATOM	3397	O	THR	A	363	73.668	34.467	18.705	1.00 38.50
ATOM	3398	N	GLY	A	364	75.660	33.438	18.763	1.00 36.22
ATOM	3400	CA	GLY	A	364	76.377	34.692	18.626	1.00 35.40
ATOM	3401	C	GLY	A	364	77.639	34.632	17.794	1.00 35.46
ATOM	3402	O	GLY	A	364	78.075	33.561	17.395	1.00 35.68
ATOM	3403	N	SER	A	365	78.216	35.795	17.522	1.00 37.37
ATOM	3405	CA	SER	A	365	79.434	35.884	16.738	1.00 39.81
ATOM	3406	CB	SER	A	365	79.399	37.121	15.840	1.00 41.52
ATOM	3407	OG	SER	A	365	78.345	37.028	14.895	1.00 50.49
ATOM	3409	C	SER	A	365	80.627	35.975	17.669	1.00 40.48
ATOM	3410	O	SER	A	365	80.584	36.669	18.682	1.00 43.48
ATOM	3411	N	MET	A	366	81.685	35.259	17.330	1.00 40.04
ATOM	3413	CA	MET	A	366	82.898	35.271	18.118	1.00 40.25
ATOM	3414	CB	MET	A	366	83.254	33.836	18.509	1.00 41.64
ATOM	3415	CG	MET	A	366	84.524	33.688	19.310	1.00 44.41
ATOM	3416	SD	MET	A	366	84.378	34.496	20.881	1.00 48.93
ATOM	3417	CE	MET	A	366	83.512	33.252	21.833	1.00 49.58
ATOM	3418	C	MET	A	366	83.978	35.880	17.224	1.00 41.24
ATOM	3419	O	MET	A	366	84.400	35.262	16.249	1.00 43.55
ATOM	3420	N	GLU	A	367	84.347	37.129	17.482	1.00 42.13
ATOM	3422	CA	GLU	A	367	85.383	37.780	16.686	1.00 43.88
ATOM	3423	CB	GLU	A	367	85.148	39.288	16.608	1.00 47.79
ATOM	3424	CG	GLU	A	367	84.094	39.715	15.588	1.00 54.26
ATOM	3425	CD	GLU	A	367	84.551	39.555	14.143	1.00 57.86
ATOM	3426	OE1	GLU	A	367	85.768	39.681	13.872	1.00 60.11
ATOM	3427	OE2	GLU	A	367	83.683	39.315	13.273	1.00 59.61
ATOM	3428	C	GLU	A	367	86.724	37.492	17.336	1.00 43.57
ATOM	3429	O	GLU	A	367	86.822	37.491	18.562	1.00 44.51

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ATOM	3430	N	VAL A 368	87.752	37.256	16.526	1.00	42.06
ATOM	3432	CA	VAL A 368	89.077	36.944	17.047	1.00	42.38
ATOM	3433	CB	VAL A 368	89.412	35.454	16.810	1.00	42.31
ATOM	3434	CG1	VAL A 368	90.866	35.167	17.146	1.00	44.40
ATOM	3435	CG2	VAL A 368	88.509	34.581	17.660	1.00	41.44
ATOM	3436	C	VAL A 368	90.204	37.822	16.491	1.00	43.82
ATOM	3437	O	VAL A 368	90.306	38.039	15.279	1.00	44.42
ATOM	3438	N	SER A 369	91.051	38.312	17.392	1.00	44.15
ATOM	3440	CA	SER A 369	92.182	39.160	17.032	1.00	46.20
ATOM	3441	CB	SER A 369	91.838	40.636	17.254	1.00	48.08
ATOM	3442	OG	SER A 369	90.692	41.011	16.508	1.00	55.65
ATOM	3444	C	SER A 369	93.376	38.773	17.896	1.00	46.39
ATOM	3445	O	SER A 369	93.269	37.897	18.757	1.00	45.59
ATOM	3446	N	ALA A 370	94.503	39.447	17.692	1.00	46.96
ATOM	3448	CA	ALA A 370	95.705	39.151	18.455	1.00	46.86
ATOM	3449	CB	ALA A 370	96.659	38.334	17.615	1.00	48.51
ATOM	3450	C	ALA A 370	96.401	40.399	18.961	1.00	47.76
ATOM	3451	O	ALA A 370	96.526	41.384	18.234	1.00	49.78
ATOM	3452	N	GLU A 371	96.833	40.346	20.215	1.00	49.05
ATOM	3454	CA	GLU A 371	97.546	41.429	20.889	1.00	52.58
ATOM	3455	CB	GLU A 371	96.670	42.035	21.999	1.00	55.47
ATOM	3456	CG	GLU A 371	97.394	42.954	23.010	1.00	61.82
ATOM	3457	CD	GLU A 371	97.662	44.365	22.494	1.00	66.05
ATOM	3458	OE1	GLU A 371	96.728	44.994	21.945	1.00	69.54
ATOM	3459	OE2	GLU A 371	98.801	44.859	22.662	1.00	66.75
ATOM	3460	C	GLU A 371	98.753	40.718	21.490	1.00	53.47
ATOM	3461	O	GLU A 371	98.617	39.613	22.015	1.00	54.95
ATOM	3462	N	SER A 372	99.926	41.337	21.418	1.00	54.76
ATOM	3464	CA	SER A 372	101.145	40.718	21.932	1.00	54.93
ATOM	3465	CB	SER A 372	101.080	40.570	23.462	1.00	56.19
ATOM	3466	OG	SER A 372	100.788	41.803	24.098	1.00	57.76
ATOM	3468	C	SER A 372	101.267	39.347	21.245	1.00	54.65
ATOM	3469	O	SER A 372	101.364	39.275	20.017	1.00	56.14
ATOM	3470	N	ASN A 373	101.207	38.271	22.023	1.00	51.39

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ATOM	3472	CA	ASN	A	373	101.292	36.922	21.480	1.00 48.43
ATOM	3473	CB	ASN	A	373	102.606	36.249	21.891	1.00 49.96
ATOM	3474	CG	ASN	A	373	103.830	36.981	21.379	1.00 51.10
ATOM	3475	OD1	ASN	A	373	103.780	37.674	20.361	1.00 53.30
ATOM	3476	ND2	ASN	A	373	104.946	36.818	22.078	1.00 50.08
ATOM	3479	C	ASN	A	373	100.126	36.168	22.087	1.00 46.52
ATOM	3480	O	ASN	A	373	100.267	35.027	22.529	1.00 45.55
ATOM	3481	N	ARG	A	374	98.983	36.838	22.156	1.00 44.90
ATOM	3483	CA	ARG	A	374	97.780	36.255	22.730	1.00 43.78
ATOM	3484	CB	ARG	A	374	97.293	37.082	23.929	1.00 45.07
ATOM	3485	CG	ARG	A	374	98.263	37.183	25.090	1.00 47.75
ATOM	3486	CD	ARG	A	374	97.653	37.976	26.235	1.00 52.92
ATOM	3487	NE	ARG	A	374	97.293	39.342	25.857	1.00 58.67
ATOM	3489	CZ	ARG	A	374	97.737	40.439	26.468	1.00 62.31
ATOM	3490	NH1	ARG	A	374	98.568	40.347	27.500	1.00 63.80
ATOM	3493	NH2	ARG	A	374	97.345	41.637	26.047	1.00 62.63
ATOM	3496	C	ARG	A	374	96.660	36.163	21.706	1.00 41.67
ATOM	3497	O	ARG	A	374	96.660	36.866	20.698	1.00 42.40
ATOM	3498	N	LEU	A	375	95.720	35.268	21.972	1.00 39.53
ATOM	3500	CA	LEU	A	375	94.568	35.063	21.119	1.00 38.25
ATOM	3501	CB	LEU	A	375	94.366	33.568	20.886	1.00 40.19
ATOM	3502	CG	LEU	A	375	93.330	33.154	19.846	1.00 42.29
ATOM	3503	CD1	LEU	A	375	93.784	33.625	18.478	1.00 42.24
ATOM	3504	CD2	LEU	A	375	93.158	31.646	19.866	1.00 41.82
ATOM	3505	C	LEU	A	375	93.399	35.623	21.917	1.00 37.82
ATOM	3506	O	LEU	A	375	93.024	35.058	22.946	1.00 38.21
ATOM	3507	N	VAL	A	376	92.871	36.764	21.491	1.00 38.16
ATOM	3509	CA	VAL	A	376	91.752	37.384	22.193	1.00 38.06
ATOM	3510	CB	VAL	A	376	92.057	38.847	22.613	1.00 37.73
ATOM	3511	CG1	VAL	A	376	93.386	38.928	23.343	1.00 36.49
ATOM	3512	CG2	VAL	A	376	92.054	39.762	21.409	1.00 37.89
ATOM	3513	C	VAL	A	376	90.517	37.376	21.313	1.00 37.85
ATOM	3514	O	VAL	A	376	90.615	37.251	20.091	1.00 37.84

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ATOM	3515	N	GLY	A	377	89.358	37.542	21.935	1.00 38.79
ATOM	3517	CA	GLY	A	377	88.120	37.548	21.186	1.00 38.96
ATOM	3518	C	GLY	A	377	87.034	38.334	21.880	1.00 38.86
ATOM	3519	O	GLY	A	377	87.235	38.860	22.976	1.00 40.46
ATOM	3520	N	GLU	A	378	85.881	38.426	21.235	1.00 39.21
ATOM	3522	CA	GLU	A	378	84.752	39.143	21.793	1.00 39.89
ATOM	3523	CB	GLU	A	378	84.762	40.601	21.335	1.00 42.06
ATOM	3524	CG	GLU	A	378	83.935	41.522	22.226	1.00 47.89
ATOM	3525	CD	GLU	A	378	83.384	42.725	21.488	1.00 51.11
ATOM	3526	OE1	GLU	A	378	84.142	43.357	20.718	1.00 53.99
ATOM	3527	OE2	GLU	A	378	82.184	43.031	21.679	1.00 52.17
ATOM	3528	C	GLU	A	378	83.481	38.456	21.315	1.00 40.11
ATOM	3529	O	GLU	A	378	83.352	38.132	20.133	1.00 40.78
ATOM	3530	N	LEU	A	379	82.569	38.211	22.249	1.00 40.26
ATOM	3532	CA	LEU	A	379	81.297	37.558	21.973	1.00 41.54
ATOM	3533	CB	LEU	A	379	80.935	36.651	23.155	1.00 43.08
ATOM	3534	CG	LEU	A	379	80.208	35.314	22.991	1.00 45.34
ATOM	3535	CD1	LEU	A	379	79.839	34.798	24.377	1.00 44.87
ATOM	3536	CD2	LEU	A	379	78.966	35.444	22.136	1.00 44.17
ATOM	3537	C	LEU	A	379	80.199	38.613	21.799	1.00 42.68
ATOM	3538	O	LEU	A	379	80.179	39.623	22.507	1.00 43.44
ATOM	3539	N	LYS	A	380	79.303	38.384	20.845	1.00 44.09
ATOM	3541	CA	LYS	A	380	78.171	39.276	20.588	1.00 46.18
ATOM	3542	CB	LYS	A	380	78.438	40.165	19.373	1.00 48.46
ATOM	3543	CG	LYS	A	380	79.444	41.279	19.660	1.00 54.25
ATOM	3544	CD	LYS	A	380	79.847	42.041	18.408	1.00 58.33
ATOM	3545	CE	LYS	A	380	80.817	43.172	18.734	1.00 60.62
ATOM	3546	NZ	LYS	A	380	81.332	43.851	17.509	1.00 63.04
ATOM	3550	C	LYS	A	380	76.968	38.367	20.369	1.00 46.00
ATOM	3551	O	LYS	A	380	77.042	37.418	19.591	1.00 45.80
ATOM	3552	N	LEU	A	381	75.877	38.630	21.082	1.00 46.45
ATOM	3554	CA	LEU	A	381	74.690	37.784	20.996	1.00 46.82
ATOM	3555	CB	LEU	A	381	74.115	37.545	22.400	1.00 45.07
ATOM	3556	CG	LEU	A	381	75.001	36.992	23.521	1.00 41.15

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ATOM	3557	CD1	LEU	A	381	74.206	36.974	24.817	1.00 39.28
ATOM	3558	CD2	LEU	A	381	75.500	35.604	23.174	1.00 40.04
ATOM	3559	C	LEU	A	381	73.569	38.272	20.084	1.00 48.41
ATOM	3560	O	LEU	A	381	73.505	39.448	19.719	1.00 48.91
ATOM	3561	N	ASP	A	382	72.696	37.335	19.725	1.00 50.06
ATOM	3563	CA	ASP	A	382	71.527	37.591	18.894	1.00 54.68
ATOM	3564	CB	ASP	A	382	71.371	36.488	17.845	1.00 57.78
ATOM	3565	CG	ASP	A	382	71.718	36.953	16.453	1.00 61.73
ATOM	3566	OD1	ASP	A	382	72.846	37.455	16.258	1.00 65.65
ATOM	3567	OD2	ASP	A	382	70.862	36.809	15.552	1.00 62.89
ATOM	3568	C	ASP	A	382	70.325	37.565	19.836	1.00 56.30
ATOM	3569	O	ASP	A	382	70.465	37.827	21.030	1.00 57.37
ATOM	3570	N	ARG	A	383	69.147	37.244	19.304	1.00 57.17
ATOM	3572	CA	ARG	A	383	67.932	37.169	20.116	1.00 56.86
ATOM	3573	CB	ARG	A	383	66.710	36.913	19.221	1.00 61.20
ATOM	3574	CG	ARG	A	383	66.368	38.054	18.262	1.00 66.61
ATOM	3575	CD	ARG	A	383	65.158	37.721	17.389	1.00 68.98
ATOM	3576	NE	ARG	A	383	64.674	38.887	16.647	1.00 73.50
ATOM	3578	CZ	ARG	A	383	64.914	39.119	15.358	1.00 76.60
ATOM	3579	NH1	ARG	A	383	65.639	38.269	14.636	1.00 77.94
ATOM	3582	NH2	ARG	A	383	64.421	40.210	14.784	1.00 77.33
ATOM	3585	C	ARG	A	383	68.081	36.026	21.120	1.00 54.61
ATOM	3586	O	ARG	A	383	68.689	35.001	20.801	1.00 56.02
ATOM	3587	N	LEU	A	384	67.565	36.207	22.333	1.00 50.19
ATOM	3589	CA	LEU	A	384	67.654	35.163	23.353	1.00 47.21
ATOM	3590	CB	LEU	A	384	67.886	35.765	24.740	1.00 45.34
ATOM	3591	CG	LEU	A	384	69.072	36.707	24.951	1.00 44.13
ATOM	3592	CD1	LEU	A	384	69.089	37.136	26.403	1.00 48.33
ATOM	3593	CD2	LEU	A	384	70.386	36.036	24.587	1.00 44.37
ATOM	3594	C	LEU	A	384	66.366	34.355	23.360	1.00 46.05
ATOM	3595	O	LEU	A	384	65.287	34.910	23.175	1.00 46.98
ATOM	3596	N	LEU	A	385	66.477	33.044	23.536	1.00 45.63
ATOM	3598	CA	LEU	A	385	65.299	32.190	23.564	1.00 44.83

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ATOM	3599	CB	LEU	A	385	65.417	31.034	22.577	1.00 47.07
ATOM	3600	CG	LEU	A	385	65.424	31.305	21.075	1.00 49.68
ATOM	3601	CD1	LEU	A	385	66.807	31.742	20.610	1.00 50.06
ATOM	3602	CD2	LEU	A	385	65.018	30.020	20.367	1.00 53.29
ATOM	3603	C	LEU	A	385	65.093	31.624	24.948	1.00 43.70
ATOM	3604	O	LEU	A	385	65.973	30.965	25.500	1.00 46.13
ATOM	3605	N	LEU	A	386	63.921	31.879	25.501	1.00 41.90
ATOM	3607	CA	LEU	A	386	63.586	31.399	26.819	1.00 40.93
ATOM	3608	CB	LEU	A	386	62.804	32.467	27.576	1.00 38.95
ATOM	3609	CG	LEU	A	386	63.610	33.573	28.251	1.00 38.87
ATOM	3610	CD1	LEU	A	386	64.732	34.076	27.364	1.00 36.69
ATOM	3611	CD2	LEU	A	386	62.671	34.690	28.636	1.00 38.24
ATOM	3612	C	LEU	A	386	62.754	30.140	26.711	1.00 41.89
ATOM	3613	O	LEU	A	386	62.154	29.861	25.677	1.00 44.73
ATOM	3614	N	GLU	A	387	62.777	29.354	27.773	1.00 42.45
ATOM	3616	CA	GLU	A	387	62.006	28.133	27.867	1.00 43.22
ATOM	3617	CB	GLU	A	387	62.773	26.932	27.306	1.00 44.48
ATOM	3618	CG	GLU	A	387	61.993	25.614	27.408	1.00 46.64
ATOM	3619	CD	GLU	A	387	62.699	24.436	26.762	1.00 48.74
ATOM	3620	OE1	GLU	A	387	62.622	24.305	25.520	1.00 53.50
ATOM	3621	OE2	GLU	A	387	63.311	23.629	27.495	1.00 48.42
ATOM	3622	C	GLU	A	387	61.791	27.966	29.359	1.00 45.59
ATOM	3623	O	GLU	A	387	62.697	28.232	30.150	1.00 47.68
ATOM	3624	N	LEU	A	388	60.574	27.618	29.750	1.00 47.18
ATOM	3626	CA	LEU	A	388	60.260	27.422	31.156	1.00 48.51
ATOM	3627	CB	LEU	A	388	58.795	27.778	31.418	1.00 49.74
ATOM	3628	CG	LEU	A	388	58.298	27.776	32.865	1.00 49.97
ATOM	3629	CD1	LEU	A	388	58.957	28.902	33.656	1.00 49.70
ATOM	3630	CD2	LEU	A	388	56.788	27.935	32.871	1.00 51.43
ATOM	3631	C	LEU	A	388	60.513	25.953	31.468	1.00 49.89
ATOM	3632	O	LEU	A	388	60.033	25.071	30.754	1.00 49.90
ATOM	3633	N	LYS	A	389	61.290	25.688	32.511	1.00 53.07
ATOM	3635	CA	LYS	A	389	61.599	24.312	32.883	1.00 57.61
ATOM	3636	CB	LYS	A	389	63.109	24.152	33.105	1.00 58.15

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ATOM	3637	CG	LYS	A	389	63.933	24.486	31.864	1.00 58.89
ATOM	3638	CD	LYS	A	389	65.377	24.022	31.971	1.00 61.45
ATOM	3639	CE	LYS	A	389	66.104	24.202	30.640	1.00 63.53
ATOM	3640	NZ	LYS	A	389	67.507	23.692	30.664	1.00 66.07
ATOM	3644	C	LYS	A	389	60.800	23.813	34.094	1.00 60.00
ATOM	3645	O	LYS	A	389	60.351	22.663	34.122	1.00 61.33
ATOM	3646	N	HIS	A	390	60.622	24.679	35.086	1.00 61.51
ATOM	3648	CA	HIS	A	390	59.871	24.347	36.297	1.00 63.22
ATOM	3649	CB	HIS	A	390	60.713	23.474	37.242	1.00 68.01
ATOM	3650	CG	HIS	A	390	59.939	22.880	38.386	1.00 74.01
ATOM	3651	CD2	HIS	A	390	59.403	21.647	38.553	1.00 76.41
ATOM	3652	ND1	HIS	A	390	59.682	23.568	39.554	1.00 76.75
ATOM	3654	CE1	HIS	A	390	59.023	22.785	40.391	1.00 78.97
ATOM	3655	NE2	HIS	A	390	58.843	21.613	39.807	1.00 79.75
ATOM	3657	C	HIS	A	390	59.551	25.669	36.969	1.00 61.81
ATOM	3658	O	HIS	A	390	60.348	26.604	36.912	1.00 62.27
ATOM	3659	N	SER	A	391	58.375	25.762	37.572	1.00 60.92
ATOM	3661	CA	SER	A	391	57.978	26.980	38.257	1.00 59.76
ATOM	3662	CB	SER	A	391	57.005	27.793	37.403	1.00 58.20
ATOM	3663	OG	SER	A	391	56.639	28.996	38.059	1.00 55.50
ATOM	3665	C	SER	A	391	57.322	26.605	39.567	1.00 59.99
ATOM	3666	O	SER	A	391	56.486	25.699	39.618	1.00 60.83
ATOM	3667	N	ASN	A	392	57.753	27.260	40.636	1.00 59.65
ATOM	3669	CA	ASN	A	392	57.190	27.008	41.949	1.00 59.99
ATOM	3670	CB	ASN	A	392	58.241	27.234	43.039	1.00 58.88
ATOM	3671	CG	ASN	A	392	59.314	26.152	43.054	1.00 58.15
ATOM	3672	OD1	ASN	A	392	59.424	25.344	42.126	1.00 59.13
ATOM	3673	ND2	ASN	A	392	60.117	26.137	44.108	1.00 57.91
ATOM	3676	C	ASN	A	392	55.976	27.914	42.145	1.00 60.50
ATOM	3677	O	ASN	A	392	55.149	27.678	43.023	1.00 61.62
ATOM	3678	N	ILE	A	393	55.851	28.926	41.288	1.00 61.07
ATOM	3680	CA	ILE	A	393	54.730	29.861	41.351	1.00 60.89
ATOM	3681	CB	ILE	A	393	55.212	31.333	41.306	1.00 58.61

SUBSTITUTE SHEET (RULE 26)

ATOM	3682	CG2	ILE	A	393	56.083	31.634	42.510	1.00 58.38
ATOM	3683	CG1	ILE	A	393	55.948	31.622	39.995	1.00 57.06
ATOM	3684	CD1	ILE	A	393	56.245	33.087	39.775	1.00 56.51
ATOM	3685	C	ILE	A	393	53.700	29.632	40.228	1.00 63.24
ATOM	3686	O	ILE	A	393	53.049	30.574	39.772	1.00 64.68
ATOM	3687	N	GLY	A	394	53.556	28.382	39.786	1.00 64.29
ATOM	3689	CA	GLY	A	394	52.603	28.061	38.731	1.00 62.76
ATOM	3690	C	GLY	A	394	53.046	28.426	37.323	1.00 62.37
ATOM	3691	O	GLY	A	394	53.985	29.202	37.147	1.00 62.54
ATOM	3692	N	PRO	A	395	52.412	27.848	36.291	1.00 62.40
ATOM	3693	CD	PRO	A	395	51.333	26.846	36.373	1.00 63.52
ATOM	3694	CA	PRO	A	395	52.758	28.130	34.894	1.00 60.73
ATOM	3695	CB	PRO	A	395	51.937	27.095	34.125	1.00 61.59
ATOM	3696	CG	PRO	A	395	50.728	26.910	34.992	1.00 63.08
ATOM	3697	C	PRO	A	395	52.405	29.554	34.470	1.00 59.25
ATOM	3698	O	PRO	A	395	51.353	30.081	34.834	1.00 59.47
ATOM	3699	N	PHE	A	396	53.295	30.171	33.702	1.00 57.50
ATOM	3701	CA	PHE	A	396	53.087	31.530	33.220	1.00 55.80
ATOM	3702	CB	PHE	A	396	53.684	32.555	34.200	1.00 54.39
ATOM	3703	CG	PHE	A	396	55.194	32.588	34.223	1.00 51.73
ATOM	3704	CD1	PHE	A	396	55.899	33.426	33.364	1.00 49.07
ATOM	3705	CD2	PHE	A	396	55.909	31.796	35.115	1.00 50.73
ATOM	3706	CE1	PHE	A	396	57.283	33.474	33.394	1.00 47.56
ATOM	3707	CE2	PHE	A	396	57.295	31.841	35.150	1.00 47.47
ATOM	3708	CZ	PHE	A	396	57.981	32.678	34.289	1.00 47.02
ATOM	3709	C	PHE	A	396	53.720	31.674	31.839	1.00 55.76
ATOM	3710	O	PHE	A	396	54.463	30.792	31.392	1.00 56.39
ATOM	3711	N	PRO	A	397	53.394	32.763	31.120	1.00 54.61
ATOM	3712	CD	PRO	A	397	52.354	33.768	31.393	1.00 54.50
ATOM	3713	CA	PRO	A	397	53.966	32.967	29.787	1.00 53.13
ATOM	3714	CB	PRO	A	397	53.167	34.159	29.252	1.00 53.76
ATOM	3715	CG	PRO	A	397	51.877	34.095	30.011	1.00 53.30
ATOM	3716	C	PRO	A	397	55.448	33.301	29.899	1.00 51.99
ATOM	3717	O	PRO	A	397	55.810	34.434	30.219	1.00 51.04

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ATOM	3718	N	VAL	A	398	56.300	32.322	29.609	1.00 50.99
ATOM	3720	CA	VAL	A	398	57.747	32.506	29.686	1.00 50.88
ATOM	3721	CB	VAL	A	398	58.500	31.222	29.253	1.00 50.94
ATOM	3722	CG1	VAL	A	398	58.260	30.926	27.785	1.00 50.60
ATOM	3723	CG2	VAL	A	398	59.987	31.340	29.561	1.00 49.69
ATOM	3724	C	VAL	A	398	58.248	33.709	28.888	1.00 51.53
ATOM	3725	O	VAL	A	398	59.383	34.144	29.053	1.00 54.45
ATOM	3726	N	GLU	A	399	57.385	34.268	28.050	1.00 52.68
ATOM	3728	CA	GLU	A	399	57.741	35.427	27.236	1.00 52.46
ATOM	3729	CB	GLU	A	399	56.807	35.533	26.020	1.00 53.50
ATOM	3730	CG	GLU	A	399	56.637	34.234	25.210	1.00 53.56
ATOM	3731	CD	GLU	A	399	55.420	33.405	25.629	1.00 53.53
ATOM	3732	OE1	GLU	A	399	54.313	33.979	25.741	1.00 54.16
ATOM	3733	OE2	GLU	A	399	55.562	32.176	25.821	1.00 52.27
ATOM	3734	C	GLU	A	399	57.737	36.750	28.025	1.00 51.41
ATOM	3735	O	GLU	A	399	58.233	37.762	27.539	1.00 52.41
ATOM	3736	N	LEU	A	400	57.186	36.747	29.235	1.00 49.79
ATOM	3738	CA	LEU	A	400	57.148	37.955	30.060	1.00 49.44
ATOM	3739	CB	LEU	A	400	56.186	37.769	31.238	1.00 50.82
ATOM	3740	CG	LEU	A	400	54.683	38.030	31.086	1.00 49.58
ATOM	3741	CD1	LEU	A	400	54.427	39.510	30.867	1.00 50.78
ATOM	3742	CD2	LEU	A	400	54.114	37.220	29.954	1.00 50.81
ATOM	3743	C	LEU	A	400	58.539	38.330	30.589	1.00 50.26
ATOM	3744	O	LEU	A	400	58.800	39.487	30.931	1.00 50.71
ATOM	3745	N	LEU	A	401	59.428	37.344	30.656	1.00 50.41
ATOM	3747	CA	LEU	A	401	60.790	37.548	31.143	1.00 49.44
ATOM	3748	CB	LEU	A	401	61.310	36.255	31.766	1.00 48.32
ATOM	3749	CG	LEU	A	401	60.598	35.840	33.049	1.00 46.40
ATOM	3750	CD1	LEU	A	401	60.738	34.361	33.262	1.00 45.30
ATOM	3751	CD2	LEU	A	401	61.168	36.620	34.218	1.00 48.02
ATOM	3752	C	LEU	A	401	61.762	38.013	30.066	1.00 49.89
ATOM	3753	O	LEU	A	401	62.919	38.303	30.360	1.00 51.08
ATOM	3754	N	GLN	A	402	61.288	38.091	28.826	1.00 51.14

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ATOM	3756	CA	GLN	A	402	62.107	38.511	27.686	1.00 52.43
ATOM	3757	CB	GLN	A	402	61.255	38.569	26.413	1.00 53.25
ATOM	3758	CG	GLN	A	402	60.908	37.211	25.810	1.00 55.42
ATOM	3759	CD	GLN	A	402	61.966	36.697	24.851	1.00 55.66
ATOM	3760	OE1	GLN	A	402	63.075	37.229	24.780	1.00 55.93
ATOM	3761	NE2	GLN	A	402	61.619	35.667	24.090	1.00 56.71
ATOM	3764	C	GLN	A	402	62.800	39.855	27.890	1.00 53.23
ATOM	3765	O	GLN	A	402	64.009	39.977	27.684	1.00 54.78
ATOM	3766	N	ASP	A	403	62.031	40.866	28.275	1.00 53.89
ATOM	3768	CA	ASP	A	403	62.578	42.198	28.505	1.00 54.40
ATOM	3769	CB	ASP	A	403	61.441	43.183	28.797	1.00 58.20
ATOM	3770	CG	ASP	A	403	60.524	43.394	27.597	1.00 60.37
ATOM	3771	OD1	ASP	A	403	61.001	43.915	26.563	1.00 60.48
ATOM	3772	OD2	ASP	A	403	59.325	43.045	27.691	1.00 61.61
ATOM	3773	C	ASP	A	403	63.615	42.204	29.638	1.00 53.27
ATOM	3774	O	ASP	A	403	64.669	42.836	29.525	1.00 53.59
ATOM	3775	N	ILE	A	404	63.318	41.487	30.719	1.00 51.11
ATOM	3777	CA	ILE	A	404	64.229	41.387	31.852	1.00 48.30
ATOM	3778	CB	ILE	A	404	63.545	40.668	33.055	1.00 45.31
ATOM	3779	CG2	ILE	A	404	64.352	39.468	33.530	1.00 47.52
ATOM	3780	CG1	ILE	A	404	63.337	41.654	34.203	1.00 42.01
ATOM	3781	CD1	ILE	A	404	64.620	42.234	34.752	1.00 36.04
ATOM	3782	C	ILE	A	404	65.497	40.656	31.400	1.00 48.48
ATOM	3783	O	ILE	A	404	66.611	41.108	31.667	1.00 51.31
ATOM	3784	N	MET	A	405	65.318	39.564	30.660	1.00 47.51
ATOM	3786	CA	MET	A	405	66.433	38.768	30.151	1.00 47.38
ATOM	3787	CB	MET	A	405	65.920	37.479	29.505	1.00 47.17
ATOM	3788	CG	MET	A	405	66.151	36.233	30.345	1.00 48.66
ATOM	3789	SD	MET	A	405	65.913	36.487	32.115	1.00 49.07
ATOM	3790	CE	MET	A	405	67.594	36.786	32.640	1.00 50.09
ATOM	3791	C	MET	A	405	67.291	39.540	29.160	1.00 46.62
ATOM	3792	O	MET	A	405	68.500	39.339	29.092	1.00 48.06
ATOM	3793	N	ASN	A	406	66.666	40.441	28.413	1.00 46.76
ATOM	3795	CA	ASN	A	406	67.383	41.239	27.433	1.00 47.68

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ATOM	3796	CB	ASN	A	406	66.467	41.675	26.295	1.00 51.33
ATOM	3797	CG	ASN	A	406	66.534	40.732	25.115	1.00 54.24
ATOM	3798	OD1	ASN	A	406	67.448	40.813	24.290	1.00 55.58
ATOM	3799	ND2	ASN	A	406	65.580	39.814	25.039	1.00 54.80
ATOM	3802	C	ASN	A	406	68.134	42.430	27.999	1.00 46.60
ATOM	3803	O	ASN	A	406	68.803	43.148	27.263	1.00 48.59
ATOM	3804	N	TYR	A	407	67.993	42.674	29.293	1.00 45.78
ATOM	3806	CA	TYR	A	407	68.732	43.760	29.922	1.00 44.83
ATOM	3807	CB	TYR	A	407	67.825	44.613	30.829	1.00 46.29
ATOM	3808	CG	TYR	A	407	68.558	45.733	31.553	1.00 45.38
ATOM	3809	CD1	TYR	A	407	68.891	46.916	30.897	1.00 45.96
ATOM	3810	CE1	TYR	A	407	69.621	47.915	31.540	1.00 47.49
ATOM	3811	CD2	TYR	A	407	68.966	45.582	32.880	1.00 45.49
ATOM	3812	CE2	TYR	A	407	69.694	46.573	33.532	1.00 44.88
ATOM	3813	CZ	TYR	A	407	70.022	47.733	32.858	1.00 47.09
ATOM	3814	OH	TYR	A	407	70.771	48.701	33.493	1.00 48.41
ATOM	3816	C	TYR	A	407	69.837	43.080	30.730	1.00 43.05
ATOM	3817	O	TYR	A	407	71.024	43.262	30.462	1.00 42.68
ATOM	3818	N	ILE	A	408	69.423	42.229	31.661	1.00 41.43
ATOM	3820	CA	ILE	A	408	70.332	41.490	32.523	1.00 40.32
ATOM	3821	CB	ILE	A	408	69.580	40.371	33.272	1.00 40.57
ATOM	3822	CG2	ILE	A	408	70.550	39.445	33.978	1.00 42.21
ATOM	3823	CG1	ILE	A	408	68.613	40.974	34.281	1.00 41.88
ATOM	3824	CD1	ILE	A	408	67.762	39.937	34.976	1.00 46.39
ATOM	3825	C	ILE	A	408	71.480	40.861	31.746	1.00 39.97
ATOM	3826	O	ILE	A	408	72.639	41.158	32.006	1.00 40.89
ATOM	3827	N	VAL	A	409	71.155	40.027	30.767	1.00 39.94
ATOM	3829	CA	VAL	A	409	72.178	39.342	29.988	1.00 39.04
ATOM	3830	CB	VAL	A	409	71.560	38.354	28.961	1.00 38.16
ATOM	3831	CG1	VAL	A	409	72.656	37.687	28.142	1.00 37.45
ATOM	3832	CG2	VAL	A	409	70.741	37.291	29.686	1.00 36.14
ATOM	3833	C	VAL	A	409	73.252	40.227	29.343	1.00 38.82
ATOM	3834	O	VAL	A	409	74.426	40.093	29.675	1.00 39.64

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ATOM	3835	N	PRO	A	410	72.881	41.145	28.432	1.00 38.89
ATOM	3836	CD	PRO	A	410	71.583	41.362	27.770	1.00 38.55
ATOM	3837	CA	PRO	A	410	73.917	41.984	27.818	1.00 38.75
ATOM	3838	CB	PRO	A	410	73.207	42.562	26.597	1.00 38.19
ATOM	3839	CG	PRO	A	410	71.806	42.667	27.051	1.00 38.80
ATOM	3840	C	PRO	A	410	74.535	43.083	28.685	1.00 40.43
ATOM	3841	O	PRO	A	410	75.607	43.593	28.359	1.00 41.27
ATOM	3842	N	ILE	A	411	73.870	43.461	29.771	1.00 41.44
ATOM	3844	CA	ILE	A	411	74.404	44.503	30.649	1.00 41.02
ATOM	3845	CB	ILE	A	411	73.285	45.380	31.239	1.00 40.99
ATOM	3846	CG2	ILE	A	411	73.890	46.497	32.086	1.00 41.83
ATOM	3847	CG1	ILE	A	411	72.418	45.967	30.122	1.00 42.47
ATOM	3848	CD1	ILE	A	411	73.112	47.005	29.264	1.00 45.28
ATOM	3849	C	ILE	A	411	75.212	43.923	31.809	1.00 40.15
ATOM	3850	O	ILE	A	411	76.254	44.460	32.186	1.00 39.92
ATOM	3851	N	LEU	A	412	74.716	42.831	32.379	1.00 39.13
ATOM	3853	CA	LEU	A	412	75.373	42.185	33.506	1.00 39.13
ATOM	3854	CB	LEU	A	412	74.335	41.817	34.570	1.00 39.71
ATOM	3855	CG	LEU	A	412	73.493	42.941	35.179	1.00 38.70
ATOM	3856	CD1	LEU	A	412	72.548	42.362	36.220	1.00 36.24
ATOM	3857	CD2	LEU	A	412	74.403	43.986	35.802	1.00 39.15
ATOM	3858	C	LEU	A	412	76.209	40.945	33.175	1.00 39.67
ATOM	3859	O	LEU	A	412	77.322	40.796	33.677	1.00 41.17
ATOM	3860	N	VAL	A	413	75.678	40.060	32.336	1.00 38.13
ATOM	3862	CA	VAL	A	413	76.369	38.818	31.991	1.00 37.18
ATOM	3863	CB	VAL	A	413	75.344	37.708	31.642	1.00 38.08
ATOM	3864	CG1	VAL	A	413	76.042	36.373	31.445	1.00 39.08
ATOM	3865	CG2	VAL	A	413	74.303	37.591	32.753	1.00 35.49
ATOM	3866	C	VAL	A	413	77.477	38.893	30.926	1.00 36.23
ATOM	3867	O	VAL	A	413	78.634	38.583	31.221	1.00 36.97
ATOM	3868	N	LEU	A	414	77.134	39.296	29.702	1.00 34.70
ATOM	3870	CA	LEU	A	414	78.108	39.394	28.610	1.00 32.37
ATOM	3871	CB	LEU	A	414	77.500	40.081	27.390	1.00 31.45
ATOM	3872	CG	LEU	A	414	77.451	39.326	26.062	1.00 31.86

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ATOM	3873	CD1	LEU	A	414	77.167	40.338	24.952	1.00 34.05
ATOM	3874	CD2	LEU	A	414	78.751	38.585	25.790	1.00 30.36
ATOM	3875	C	LEU	A	414	79.403	40.109	28.972	1.00 33.92
ATOM	3876	O	LEU	A	414	80.485	39.643	28.619	1.00 36.82
ATOM	3877	N	PRO	A	415	79.314	41.285	29.619	1.00 34.56
ATOM	3878	CD	PRO	A	415	78.103	42.090	29.858	1.00 34.83
ATOM	3879	CA	PRO	A	415	80.503	42.046	30.011	1.00 35.76
ATOM	3880	CB	PRO	A	415	79.915	43.149	30.883	1.00 35.11
ATOM	3881	CG	PRO	A	415	78.673	43.467	30.151	1.00 35.76
ATOM	3882	C	PRO	A	415	81.583	41.263	30.748	1.00 36.22
ATOM	3883	O	PRO	A	415	82.760	41.387	30.418	1.00 37.32
ATOM	3884	N	ARG	A	416	81.194	40.466	31.739	1.00 39.00
ATOM	3886	CA	ARG	A	416	82.167	39.686	32.501	1.00 41.92
ATOM	3887	CB	ARG	A	416	81.517	39.047	33.731	1.00 46.13
ATOM	3888	CG	ARG	A	416	81.111	40.038	34.823	1.00 52.86
ATOM	3889	CD	ARG	A	416	82.299	40.830	35.366	1.00 60.47
ATOM	3890	NE	ARG	A	416	83.287	39.986	36.040	1.00 69.03
ATOM	3892	CZ	ARG	A	416	83.205	39.589	37.309	1.00 73.10
ATOM	3893	NH1	ARG	A	416	82.174	39.955	38.062	1.00 76.24
ATOM	3896	NH2	ARG	A	416	84.163	38.833	37.834	1.00 73.45
ATOM	3899	C	ARG	A	416	82.826	38.622	31.636	1.00 42.34
ATOM	3900	O	ARG	A	416	84.031	38.405	31.717	1.00 43.31
ATOM	3901	N	VAL	A	417	82.040	37.990	30.774	1.00 42.15
ATOM	3903	CA	VAL	A	417	82.554	36.955	29.886	1.00 41.06
ATOM	3904	CB	VAL	A	417	81.418	36.302	29.091	1.00 43.59
ATOM	3905	CG1	VAL	A	417	81.976	35.261	28.127	1.00 48.62
ATOM	3906	CG2	VAL	A	417	80.414	35.672	30.038	1.00 45.02
ATOM	3907	C	VAL	A	417	83.581	37.500	28.902	1.00 38.49
ATOM	3908	O	VAL	A	417	84.658	36.929	28.729	1.00 38.46
ATOM	3909	N	ASN	A	418	83.236	38.598	28.243	1.00 36.89
ATOM	3911	CA	ASN	A	418	84.130	39.206	27.273	1.00 34.67
ATOM	3912	CB	ASN	A	418	83.448	40.370	26.564	1.00 36.25
ATOM	3913	CG	ASN	A	418	82.506	39.913	25.475	1.00 37.58

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ATOM	3914	OD1	ASN	A	418	82.585	38.776	25.014	1.00 39.99
ATOM	3915	ND2	ASN	A	418	81.613	40.796	25.055	1.00 36.92
ATOM	3918	C	ASN	A	418	85.426	39.671	27.896	1.00 34.68
ATOM	3919	O	ASN	A	418	86.421	39.831	27.199	1.00 35.38
ATOM	3920	N	GLU	A	419	85.426	39.895	29.206	1.00 35.06
ATOM	3922	CA	GLU	A	419	86.640	40.336	29.879	1.00 37.31
ATOM	3923	CB	GLU	A	419	86.351	40.788	31.304	1.00 41.20
ATOM	3924	CG	GLU	A	419	87.557	41.433	31.972	1.00 49.99
ATOM	3925	CD	GLU	A	419	87.312	41.800	33.419	1.00 54.63
ATOM	3926	OE1	GLU	A	419	86.182	42.226	33.751	1.00 59.06
ATOM	3927	OE2	GLU	A	419	88.257	41.666	34.227	1.00 59.31
ATOM	3928	C	GLU	A	419	87.682	39.222	29.889	1.00 37.58
ATOM	3929	O	GLU	A	419	88.882	39.486	29.785	1.00 38.06
ATOM	3930	N	LYS	A	420	87.232	37.980	30.049	1.00 37.28
ATOM	3932	CA	LYS	A	420	88.154	36.853	30.033	1.00 37.63
ATOM	3933	CB	LYS	A	420	87.492	35.591	30.587	1.00 37.80
ATOM	3934	CG	LYS	A	420	88.379	34.342	30.510	1.00 43.22
ATOM	3935	CD	LYS	A	420	89.698	34.521	31.265	1.00 46.31
ATOM	3936	CE	LYS	A	420	90.650	33.352	31.031	1.00 48.33
ATOM	3937	NZ	LYS	A	420	91.993	33.578	31.644	1.00 48.07
ATOM	3941	C	LYS	A	420	88.610	36.631	28.593	1.00 38.72
ATOM	3942	O	LYS	A	420	89.802	36.479	28.329	1.00 41.62
ATOM	3943	N	LEU	A	421	87.663	36.659	27.657	1.00 38.62
ATOM	3945	CA	LEU	A	421	87.975	36.466	26.246	1.00 38.52
ATOM	3946	CB	LEU	A	421	86.705	36.474	25.395	1.00 36.49
ATOM	3947	CG	LEU	A	421	85.770	35.278	25.539	1.00 34.05
ATOM	3948	CD1	LEU	A	421	84.533	35.489	24.703	1.00 31.56
ATOM	3949	CD2	LEU	A	421	86.492	34.014	25.113	1.00 36.95
ATOM	3950	C	LEU	A	421	88.941	37.525	25.744	1.00 40.94
ATOM	3951	O	LEU	A	421	89.797	37.237	24.917	1.00 43.18
ATOM	3952	N	GLN	A	422	88.783	38.756	26.218	1.00 44.55
ATOM	3954	CA	GLN	A	422	89.672	39.844	25.820	1.00 48.56
ATOM	3955	CB	GLN	A	422	89.036	41.210	26.101	1.00 52.32
ATOM	3956	CG	GLN	A	422	88.278	41.821	24.914	1.00 58.07

SUBSTITUTE SHEET (RULE 26)

ATOM	3957	CD	GLN	A	422	89.197	42.459	23.863	1.00 62.49
ATOM	3958	OE1	GLN	A	422	90.361	42.770	24.133	1.00 63.36
ATOM	3959	NE2	GLN	A	422	88.661	42.673	22.665	1.00 63.04
ATOM	3962	C	GLN	A	422	91.037	39.725	26.501	1.00 49.05
ATOM	3963	O	GLN	A	422	92.013	40.323	26.045	1.00 50.57
ATOM	3964	N	LYS	A	423	91.096	38.996	27.615	1.00 49.71
ATOM	3966	CA	LYS	A	423	92.366	38.777	28.305	1.00 50.46
ATOM	3967	CB	LYS	A	423	92.151	38.125	29.670	1.00 52.85
ATOM	3968	CG	LYS	A	423	93.442	37.862	30.434	1.00 56.39
ATOM	3969	CD	LYS	A	423	93.156	37.388	31.845	1.00 59.26
ATOM	3970	CE	LYS	A	423	92.354	38.432	32.611	1.00 60.80
ATOM	3971	NZ	LYS	A	423	92.070	37.998	34.006	1.00 64.66
ATOM	3975	C	LYS	A	423	93.108	37.827	27.378	1.00 49.36
ATOM	3976	O	LYS	A	423	94.320	37.945	27.174	1.00 51.82
ATOM	3977	N	GLY	A	424	92.349	36.884	26.824	1.00 46.45
ATOM	3979	CA	GLY	A	424	92.883	35.939	25.868	1.00 40.64
ATOM	3980	C	GLY	A	424	93.484	34.658	26.377	1.00 38.23
ATOM	3981	O	GLY	A	424	93.364	34.303	27.552	1.00 36.91
ATOM	3982	N	PHE	A	425	94.111	33.950	25.445	1.00 36.95
ATOM	3984	CA	PHE	A	425	94.768	32.684	25.712	1.00 34.69
ATOM	3985	CB	PHE	A	425	93.986	31.530	25.075	1.00 38.25
ATOM	3986	CG	PHE	A	425	92.570	31.402	25.571	1.00 44.42
ATOM	3987	CD1	PHE	A	425	92.294	31.343	26.937	1.00 44.31
ATOM	3988	CD2	PHE	A	425	91.508	31.345	24.671	1.00 46.34
ATOM	3989	CE1	PHE	A	425	90.986	31.235	27.399	1.00 45.62
ATOM	3990	CE2	PHE	A	425	90.192	31.236	25.125	1.00 48.05
ATOM	3991	CZ	PHE	A	425	89.933	31.181	26.492	1.00 46.50
ATOM	3992	C	PHE	A	425	96.153	32.748	25.091	1.00 31.44
ATOM	3993	O	PHE	A	425	96.316	33.236	23.982	1.00 31.46
ATOM	3994	N	PRO	A	426	97.176	32.316	25.831	1.00 29.84
ATOM	3995	CD	PRO	A	426	97.076	31.978	27.259	1.00 30.24
ATOM	3996	CA	PRO	A	426	98.571	32.299	25.396	1.00 30.20
ATOM	3997	CB	PRO	A	426	99.269	31.630	26.570	1.00 28.60

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ATOM	3998	CG	PRO	A	426	98.494	32.133	27.725	1.00 31.57
ATOM	3999	C	PRO	A	426	98.777	31.489	24.123	1.00 31.10
ATOM	4000	O	PRO	A	426	98.258	30.377	23.998	1.00 34.08
ATOM	4001	N	LEU	A	427	99.570	32.033	23.203	1.00 29.97
ATOM	4003	CA	LEU	A	427	99.878	31.377	21.935	1.00 29.50
ATOM	4004	CB	LEU	A	427	99.991	32.433	20.831	1.00 28.79
ATOM	4005	CG	LEU	A	427	99.106	32.365	19.576	1.00 31.67
ATOM	4006	CD1	LEU	A	427	97.713	31.822	19.854	1.00 29.49
ATOM	4007	CD2	LEU	A	427	99.020	33.753	18.977	1.00 30.38
ATOM	4008	C	LEU	A	427	101.189	30.602	22.095	1.00 28.95
ATOM	4009	O	LEU	A	427	102.012	30.939	22.943	1.00 30.17
ATOM	4010	N	PRO	A	428	101.396	29.548	21.293	1.00 29.54
ATOM	4011	CD	PRO	A	428	100.502	29.048	20.234	1.00 29.81
ATOM	4012	CA	PRO	A	428	102.614	28.734	21.368	1.00 31.77
ATOM	4013	CB	PRO	A	428	102.218	27.492	20.584	1.00 30.20
ATOM	4014	CG	PRO	A	428	101.382	28.073	19.490	1.00 27.41
ATOM	4015	C	PRO	A	428	103.843	29.405	20.753	1.00 35.74
ATOM	4016	O	PRO	A	428	104.361	28.950	19.731	1.00 39.47
ATOM	4017	N	THR	A	429	104.323	30.472	21.379	1.00 36.82
ATOM	4019	CA	THR	A	429	105.486	31.189	20.866	1.00 36.58
ATOM	4020	CB	THR	A	429	105.200	32.694	20.735	1.00 38.98
ATOM	4021	OG1	THR	A	429	104.616	33.183	21.953	1.00 37.38
ATOM	4023	CG2	THR	A	429	104.262	32.956	19.565	1.00 41.95
ATOM	4024	C	THR	A	429	106.686	31.024	21.769	1.00 35.72
ATOM	4025	O	THR	A	429	106.567	31.108	22.994	1.00 35.83
ATOM	4026	N	PRO	A	430	107.867	30.791	21.182	1.00 34.72
ATOM	4027	CD	PRO	A	430	108.180	30.643	19.753	1.00 36.21
ATOM	4028	CA	PRO	A	430	109.069	30.629	21.995	1.00 34.61
ATOM	4029	CB	PRO	A	430	110.124	30.235	20.963	1.00 33.90
ATOM	4030	CG	PRO	A	430	109.658	30.907	19.726	1.00 33.59
ATOM	4031	C	PRO	A	430	109.388	31.946	22.691	1.00 35.01
ATOM	4032	O	PRO	A	430	108.648	32.924	22.553	1.00 37.38
ATOM	4033	N	ALA	A	431	110.457	31.973	23.471	1.00 34.16
ATOM	4035	CA	ALA	A	431	110.824	33.190	24.173	1.00 36.53

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ATOM	4036	CB	ALA A 431	111.801	32.878	25.298	1.00	36.36
ATOM	4037	C	ALA A 431	111.416	34.241	23.243	1.00	38.15
ATOM	4038	O	ALA A 431	111.944	33.932	22.174	1.00	39.81
ATOM	4039	N	ARG A 432	111.270	35.495	23.641	1.00	40.43
ATOM	4041	CA	ARG A 432	111.819	36.620	22.902	1.00	41.66
ATOM	4042	CB	ARG A 432	113.349	36.537	22.887	1.00	44.65
ATOM	4043	CG	ARG A 432	113.990	36.686	24.262	1.00	51.96
ATOM	4044	CD	ARG A 432	115.516	36.654	24.185	1.00	59.79
ATOM	4045	NE	ARG A 432	116.029	35.372	23.700	1.00	63.72
ATOM	4047	CZ	ARG A 432	117.302	34.993	23.777	1.00	67.96
ATOM	4048	NH1	ARG A 432	118.212	35.795	24.320	1.00	70.88
ATOM	4051	NH2	ARG A 432	117.668	33.804	23.314	1.00	68.07
ATOM	4054	C	ARG A 432	111.293	36.898	21.499	1.00	40.87
ATOM	4055	O	ARG A 432	111.963	37.567	20.721	1.00	42.99
ATOM	4056	N	VAL A 433	110.103	36.414	21.166	1.00	40.50
ATOM	4058	CA	VAL A 433	109.538	36.693	19.847	1.00	39.69
ATOM	4059	CB	VAL A 433	109.325	35.415	18.982	1.00	39.93
ATOM	4060	CG1	VAL A 433	110.588	34.575	18.943	1.00	39.03
ATOM	4061	CG2	VAL A 433	108.134	34.608	19.470	1.00	39.91
ATOM	4062	C	VAL A 433	108.206	37.399	20.024	1.00	41.27
ATOM	4063	O	VAL A 433	107.538	37.240	21.048	1.00	43.57
ATOM	4064	N	GLN A 434	107.845	38.223	19.053	1.00	41.32
ATOM	4066	CA	GLN A 434	106.583	38.939	19.104	1.00	41.91
ATOM	4067	CB	GLN A 434	106.802	40.411	19.454	1.00	45.76
ATOM	4068	CG	GLN A 434	105.706	41.018	20.335	1.00	52.61
ATOM	4069	CD	GLN A 434	105.850	40.687	21.829	1.00	56.74
ATOM	4070	OE1	GLN A 434	105.372	41.436	22.681	1.00	58.13
ATOM	4071	NE2	GLN A 434	106.512	39.579	22.149	1.00	57.45
ATOM	4074	C	GLN A 434	106.005	38.804	17.716	1.00	40.30
ATOM	4075	O	GLN A 434	106.745	38.821	16.732	1.00	40.86
ATOM	4076	N	LEU A 435	104.695	38.614	17.642	1.00	39.20
ATOM	4078	CA	LEU A 435	104.018	38.439	16.366	1.00	39.99
ATOM	4079	CB	LEU A 435	102.965	37.338	16.501	1.00	38.11

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ATOM	4080	CG	LEU	A	435	103.347	36.088	17.309	1.00 37.55
ATOM	4081	CD1	LEU	A	435	102.118	35.238	17.538	1.00 37.75
ATOM	4082	CD2	LEU	A	435	104.426	35.281	16.613	1.00 36.46
ATOM	4083	C	LEU	A	435	103.358	39.739	15.916	1.00 41.18
ATOM	4084	O	LEU	A	435	102.660	40.387	16.695	1.00 42.90
ATOM	4085	N	TYR	A	436	103.590	40.125	14.665	1.00 42.57
ATOM	4087	CA	TYR	A	436	103.004	41.348	14.116	1.00 43.80
ATOM	4088	CB	TYR	A	436	104.021	42.510	14.120	1.00 43.48
ATOM	4089	CG	TYR	A	436	105.232	42.328	13.224	1.00 43.66
ATOM	4090	CD1	TYR	A	436	106.259	41.452	13.573	1.00 43.96
ATOM	4091	CE1	TYR	A	436	107.364	41.271	12.743	1.00 44.63
ATOM	4092	CD2	TYR	A	436	105.345	43.028	12.020	1.00 43.04
ATOM	4093	CE2	TYR	A	436	106.448	42.852	11.181	1.00 43.53
ATOM	4094	CZ	TYR	A	436	107.452	41.970	11.549	1.00 44.29
ATOM	4095	OH	TYR	A	436	108.528	41.757	10.711	1.00 44.66
ATOM	4097	C	TYR	A	436	102.457	41.090	12.712	1.00 43.77
ATOM	4098	O	TYR	A	436	102.729	40.046	12.122	1.00 45.49
ATOM	4099	N	ASN	A	437	101.687	42.042	12.189	1.00 45.09
ATOM	4101	CA	ASN	A	437	101.069	41.932	10.865	1.00 45.97
ATOM	4102	CB	ASN	A	437	102.083	42.231	9.750	1.00 51.76
ATOM	4103	CG	ASN	A	437	102.161	43.720	9.416	1.00 57.75
ATOM	4104	OD1	ASN	A	437	102.832	44.492	10.105	1.00 59.59
ATOM	4105	ND2	ASN	A	437	101.450	44.131	8.370	1.00 60.25
ATOM	4108	C	ASN	A	437	100.385	40.581	10.665	1.00 44.47
ATOM	4109	O	ASN	A	437	100.743	39.797	9.786	1.00 44.02
ATOM	4110	N	VAL	A	438	99.360	40.344	11.475	1.00 44.00
ATOM	4112	CA	VAL	A	438	98.622	39.091	11.444	1.00 43.09
ATOM	4113	CB	VAL	A	438	98.214	38.646	12.871	1.00 43.35
ATOM	4114	CG1	VAL	A	438	99.425	38.629	13.786	1.00 43.74
ATOM	4115	CG2	VAL	A	438	97.143	39.562	13.433	1.00 43.99
ATOM	4116	C	VAL	A	438	97.374	39.101	10.579	1.00 41.42
ATOM	4117	O	VAL	A	438	96.740	40.139	10.377	1.00 39.58
ATOM	4118	N	VAL	A	439	97.018	37.912	10.110	1.00 41.86
ATOM	4120	CA	VAL	A	439	95.839	37.689	9.291	1.00 43.18

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ATOM	4121	CB	VAL	A	439	96.202	37.377	7.829	1.00 42.54
ATOM	4122	CG1	VAL	A	439	96.568	38.646	7.104	1.00 46.06
ATOM	4123	CG2	VAL	A	439	97.351	36.391	7.770	1.00 41.82
ATOM	4124	C	VAL	A	439	95.117	36.482	9.866	1.00 43.37
ATOM	4125	O	VAL	A	439	95.733	35.446	10.103	1.00 45.02
ATOM	4126	N	LEU	A	440	93.829	36.631	10.141	1.00 43.45
ATOM	4128	CA	LEU	A	440	93.041	35.535	10.681	1.00 42.92
ATOM	4129	CB	LEU	A	440	92.355	35.956	11.978	1.00 42.49
ATOM	4130	CG	LEU	A	440	93.220	36.062	13.234	1.00 42.93
ATOM	4131	CD1	LEU	A	440	93.920	34.745	13.462	1.00 44.28
ATOM	4132	CD2	LEU	A	440	94.231	37.181	13.111	1.00 45.59
ATOM	4133	C	LEU	A	440	92.008	35.132	9.643	1.00 44.03
ATOM	4134	O	LEU	A	440	91.017	35.831	9.446	1.00 45.13
ATOM	4135	N	GLN	A	441	92.268	34.029	8.947	1.00 44.00
ATOM	4137	CA	GLN	A	441	91.363	33.536	7.910	1.00 43.66
ATOM	4138	CB	GLN	A	441	92.148	33.058	6.678	1.00 48.64
ATOM	4139	CG	GLN	A	441	92.881	34.113	5.860	1.00 54.68
ATOM	4140	CD	GLN	A	441	93.556	33.515	4.627	1.00 57.71
ATOM	4141	OE1	GLN	A	441	93.111	32.495	4.093	1.00 59.57
ATOM	4142	NE2	GLN	A	441	94.637	34.141	4.179	1.00 60.18
ATOM	4145	C	GLN	A	441	90.528	32.355	8.390	1.00 41.14
ATOM	4146	O	GLN	A	441	91.055	31.249	8.541	1.00 41.88
ATOM	4147	N	PRO	A	442	89.217	32.553	8.613	1.00 38.75
ATOM	4148	CD	PRO	A	442	88.444	33.805	8.553	1.00 39.00
ATOM	4149	CA	PRO	A	442	88.372	31.442	9.065	1.00 35.99
ATOM	4150	CB	PRO	A	442	87.049	32.131	9.381	1.00 36.27
ATOM	4151	CG	PRO	A	442	87.038	33.295	8.450	1.00 38.58
ATOM	4152	C	PRO	A	442	88.234	30.403	7.952	1.00 34.89
ATOM	4153	O	PRO	A	442	88.109	30.751	6.780	1.00 37.34
ATOM	4154	N	HIS	A	443	88.332	29.130	8.317	1.00 32.88
ATOM	4156	CA	HIS	A	443	88.242	28.036	7.361	1.00 30.71
ATOM	4157	CB	HIS	A	443	89.610	27.377	7.172	1.00 31.17
ATOM	4158	CG	HIS	A	443	90.508	28.103	6.225	1.00 29.53

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ATOM	4159	CD2	HIS	A	443	91.098	27.702	5.076	1.00 27.37
ATOM	4160	ND1	HIS	A	443	90.868	29.421	6.400	1.00 31.12
ATOM	4162	CE1	HIS	A	443	91.635	29.804	5.397	1.00 30.58
ATOM	4163	NE2	HIS	A	443	91.790	28.779	4.580	1.00 29.90
ATOM	4165	C	HIS	A	443	87.263	27.003	7.863	1.00 31.31
ATOM	4166	O	HIS	A	443	86.698	27.157	8.936	1.00 36.03
ATOM	4167	N	GLN	A	444	87.058	25.948	7.086	1.00 33.00
ATOM	4169	CA	GLN	A	444	86.136	24.896	7.481	1.00 33.08
ATOM	4170	CB	GLN	A	444	85.802	24.000	6.282	1.00 35.23
ATOM	4171	CG	GLN	A	444	84.829	22.860	6.570	1.00 37.52
ATOM	4172	CD	GLN	A	444	83.436	23.337	6.954	1.00 41.28
ATOM	4173	OE1	GLN	A	444	83.142	24.531	6.941	1.00 42.98
ATOM	4174	NE2	GLN	A	444	82.570	22.395	7.298	1.00 44.68
ATOM	4177	C	GLN	A	444	86.735	24.069	8.613	1.00 32.22
ATOM	4178	O	GLN	A	444	87.720	23.360	8.416	1.00 34.24
ATOM	4179	N	ASN	A	445	86.175	24.230	9.808	1.00 29.86
ATOM	4181	CA	ASN	A	445	86.584	23.492	11.003	1.00 28.34
ATOM	4182	CB	ASN	A	445	86.628	21.984	10.714	1.00 27.65
ATOM	4183	CG	ASN	A	445	85.272	21.427	10.319	1.00 28.84
ATOM	4184	OD1	ASN	A	445	85.155	20.637	9.385	1.00 33.08
ATOM	4185	ND2	ASN	A	445	84.233	21.850	11.022	1.00 32.64
ATOM	4188	C	ASN	A	445	87.863	23.950	11.709	1.00 27.86
ATOM	4189	O	ASN	A	445	88.318	23.306	12.658	1.00 30.31
ATOM	4190	N	PHE	A	446	88.436	25.064	11.272	1.00 26.55
ATOM	4192	CA	PHE	A	446	89.639	25.582	11.904	1.00 25.16
ATOM	4193	CB	PHE	A	446	90.858	24.688	11.626	1.00 28.26
ATOM	4194	CG	PHE	A	446	91.407	24.796	10.233	1.00 29.75
ATOM	4195	CD1	PHE	A	446	90.953	23.956	9.223	1.00 29.14
ATOM	4196	CD2	PHE	A	446	92.413	25.711	9.940	1.00 32.05
ATOM	4197	CE1	PHE	A	446	91.492	24.020	7.950	1.00 26.24
ATOM	4198	CE2	PHE	A	446	92.961	25.784	8.662	1.00 30.94
ATOM	4199	CZ	PHE	A	446	92.500	24.936	7.667	1.00 29.55
ATOM	4200	C	PHE	A	446	89.906	27.020	11.506	1.00 25.07
ATOM	4201	O	PHE	A	446	89.372	27.508	10.513	1.00 24.16

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ATOM	4202	N	LEU	A	447	90.718	27.697	12.306	1.00 26.36
ATOM	4204	CA	LEU	A	447	91.059	29.091	12.076	1.00 25.79
ATOM	4205	CB	LEU	A	447	90.825	29.880	13.365	1.00 27.64
ATOM	4206	CG	LEU	A	447	91.097	31.384	13.422	1.00 28.75
ATOM	4207	CD1	LEU	A	447	90.193	32.125	12.449	1.00 27.40
ATOM	4208	CD2	LEU	A	447	90.863	31.875	14.843	1.00 25.78
ATOM	4209	C	LEU	A	447	92.508	29.221	11.635	1.00 25.68
ATOM	4210	O	LEU	A	447	93.398	28.619	12.223	1.00 26.90
ATOM	4211	N	LEU	A	448	92.738	30.000	10.589	1.00 26.87
ATOM	4213	CA	LEU	A	448	94.080	30.199	10.084	1.00 26.96
ATOM	4214	CB	LEU	A	448	94.074	30.247	8.559	1.00 26.42
ATOM	4215	CG	LEU	A	448	95.432	30.045	7.886	1.00 25.05
ATOM	4216	CD1	LEU	A	448	96.040	28.738	8.331	1.00 25.88
ATOM	4217	CD2	LEU	A	448	95.273	30.049	6.396	1.00 29.10
ATOM	4218	C	LEU	A	448	94.627	31.493	10.651	1.00 29.88
ATOM	4219	O	LEU	A	448	94.005	32.552	10.530	1.00 28.70
ATOM	4220	N	PHE	A	449	95.788	31.386	11.283	1.00 32.23
ATOM	4222	CA	PHE	A	449	96.469	32.511	11.897	1.00 32.39
ATOM	4223	CB	PHE	A	449	96.655	32.234	13.394	1.00 31.41
ATOM	4224	CG	PHE	A	449	97.511	33.243	14.100	1.00 31.44
ATOM	4225	CD1	PHE	A	449	98.897	33.160	14.046	1.00 32.18
ATOM	4226	CD2	PHE	A	449	96.934	34.296	14.797	1.00 35.10
ATOM	4227	CE1	PHE	A	449	99.695	34.111	14.671	1.00 32.81
ATOM	4228	CE2	PHE	A	449	97.725	35.257	15.429	1.00 34.26
ATOM	4229	CZ	PHE	A	449	99.106	35.162	15.363	1.00 33.12
ATOM	4230	C	PHE	A	449	97.829	32.685	11.228	1.00 34.46
ATOM	4231	O	PHE	A	449	98.717	31.865	11.420	1.00 38.92
ATOM	4232	N	GLY	A	450	97.990	33.738	10.439	1.00 34.70
ATOM	4234	CA	GLY	A	450	99.262	33.982	9.781	1.00 33.42
ATOM	4235	C	GLY	A	450	99.901	35.207	10.397	1.00 35.08
ATOM	4236	O	GLY	A	450	99.194	36.140	10.784	1.00 36.42
ATOM	4237	N	ALA	A	451	101.225	35.234	10.491	1.00 33.89
ATOM	4239	CA	ALA	A	451	101.889	36.383	11.092	1.00 33.95

SUBSTITUTE SHEET (RULE 26)

ATOM	4240	CB	ALA	A	451	101.649	36.384	12.587	1.00 31.78
ATOM	4241	C	ALA	A	451	103.382	36.454	10.815	1.00 34.43
ATOM	4242	O	ALA	A	451	103.986	35.489	10.335	1.00 36.02
ATOM	4243	N	ASP	A	452	103.954	37.628	11.055	1.00 33.44
ATOM	4245	CA	ASP	A	452	105.381	37.847	10.885	1.00 35.01
ATOM	4246	CB	ASP	A	452	105.670	39.186	10.196	1.00 37.76
ATOM	4247	CG	ASP	A	452	105.437	39.144	8.696	1.00 40.65
ATOM	4248	OD1	ASP	A	452	105.743	38.106	8.074	1.00 42.78
ATOM	4249	OD2	ASP	A	452	104.961	40.159	8.134	1.00 42.90
ATOM	4250	C	ASP	A	452	105.913	37.875	12.306	1.00 35.28
ATOM	4251	O	ASP	A	452	105.196	38.247	13.237	1.00 33.85
ATOM	4252	N	VAL	A	453	107.174	37.509	12.473	1.00 37.44
ATOM	4254	CA	VAL	A	453	107.771	37.468	13.798	1.00 38.73
ATOM	4255	CB	VAL	A	453	108.253	36.034	14.138	1.00 39.37
ATOM	4256	CG1	VAL	A	453	108.678	35.955	15.591	1.00 40.45
ATOM	4257	CG2	VAL	A	453	107.169	35.004	13.819	1.00 37.45
ATOM	4258	C	VAL	A	453	108.970	38.398	13.899	1.00 39.49
ATOM	4259	O	VAL	A	453	109.669	38.641	12.914	1.00 40.46
ATOM	4260	N	VAL	A	454	109.190	38.929	15.092	1.00 39.41
ATOM	4262	CA	VAL	A	454	110.324	39.796	15.331	1.00 40.55
ATOM	4263	CB	VAL	A	454	109.895	41.280	15.511	1.00 41.60
ATOM	4264	CG1	VAL	A	454	108.859	41.423	16.605	1.00 42.90
ATOM	4265	CG2	VAL	A	454	111.105	42.149	15.798	1.00 43.42
ATOM	4266	C	VAL	A	454	111.037	39.256	16.561	1.00 41.20
ATOM	4267	O	VAL	A	454	110.440	39.115	17.626	1.00 41.61
ATOM	4268	N	TYR	A	455	112.284	38.851	16.376	1.00 42.91
ATOM	4270	CA	TYR	A	455	113.084	38.309	17.460	1.00 45.62
ATOM	4271	CB	TYR	A	455	114.015	37.227	16.908	1.00 44.83
ATOM	4272	CG	TYR	A	455	115.038	36.684	17.881	1.00 44.58
ATOM	4273	CD1	TYR	A	455	114.682	35.774	18.875	1.00 43.02
ATOM	4274	CE1	TYR	A	455	115.644	35.246	19.739	1.00 44.27
ATOM	4275	CD2	TYR	A	455	116.377	37.053	17.778	1.00 46.42
ATOM	4276	CE2	TYR	A	455	117.341	36.535	18.631	1.00 46.69
ATOM	4277	CZ	TYR	A	455	116.973	35.634	19.607	1.00 46.43

SUBSTITUTE SHEET (RULE 26)

ATOM	4278	OH	TYR	A	455	117.944	35.141	20.445	1.00 49.56
ATOM	4280	C	TYR	A	455	113.864	39.443	18.128	1.00 49.88
ATOM	4281	O	TYR	A	455	114.558	40.213	17.455	1.00 49.95
ATOM	4282	N	LYS	A	456	113.694	39.552	19.444	1.00 54.41
ATOM	4284	CA	LYS	A	456	114.337	40.570	20.270	1.00 59.38
ATOM	4285	CB	LYS	A	456	113.760	40.514	21.693	1.00 61.68
ATOM	4286	CG	LYS	A	456	114.401	41.475	22.692	1.00 66.56
ATOM	4287	CD	LYS	A	456	114.016	41.153	24.140	1.00 68.38
ATOM	4288	CE	LYS	A	456	112.538	41.396	24.409	1.00 70.09
ATOM	4289	NZ	LYS	A	456	112.154	41.067	25.812	1.00 71.48
ATOM	4293	C	LYS	A	456	115.855	40.382	20.311	1.00 62.37
ATOM	4294	OT1	LYS	A	456	116.324	39.430	20.976	1.00 64.57
ATOM	4295	OT2	LYS	A	456	116.559	41.196	19.673	1.00 66.00
ATOM	4296	C1	PC	A	777	121.817	32.468	19.343	1.00 72.53
ATOM	4297	C2	PC	A	777	121.094	31.121	19.465	1.00 63.82
ATOM	4298	C3	PC	A	777	119.917	31.017	18.492	1.00 59.16
ATOM	4299	C4	PC	A	777	123.302	33.354	23.035	1.00 94.69
ATOM	4300	C5	PC	A	777	124.151	34.553	23.445	1.00 98.10
ATOM	4301	C6	PC	A	777	125.683	33.126	24.652	1.00 99.68
ATOM	4302	C7	PC	A	777	126.361	35.328	24.003	1.00100.00
ATOM	4303	C8	PC	A	777	126.086	33.627	22.335	1.00100.00
ATOM	4304	C31	PC	A	777	122.736	29.776	18.047	1.00 54.84
ATOM	4305	C32	PC	A	777	122.337	30.654	16.869	1.00 51.64
ATOM	4306	C33	PC	A	777	122.254	29.878	15.549	1.00 47.76
ATOM	4307	C34	PC	A	777	123.590	29.237	15.169	1.00 42.03
ATOM	4308	C35	PC	A	777	123.429	28.173	14.085	1.00 39.41
ATOM	4309	C36	PC	A	777	122.582	28.674	12.916	1.00 36.18
ATOM	4310	C37	PC	A	777	121.581	27.622	12.463	1.00 33.16
ATOM	4311	C38	PC	A	777	120.679	28.158	11.377	1.00 31.40
ATOM	4312	C39	PC	A	777	119.610	29.062	11.951	1.00 36.47
ATOM	4313	C40	PC	A	777	118.543	28.263	12.682	1.00 40.19
ATOM	4314	C41	PC	A	777	117.191	28.383	12.004	1.00 39.41
ATOM	4315	C42	PC	A	777	116.468	27.050	11.956	1.00 41.86

CD3+ 5 of 6 Sheet

ATOM	4316	C43	PC	A	777	115.409	26.958	13.041	1.00	43.49
ATOM	4317	C44	PC	A	777	114.326	25.951	12.669	1.00	46.22
ATOM	4318	C45	PC	A	777	113.126	26.048	13.604	1.00	47.77
ATOM	4319	C46	PC	A	777	112.271	24.786	13.561	1.00	48.67
ATOM	4320	C47	PC	A	777	111.948	24.277	14.964	1.00	48.62
ATOM	4321	C48	PC	A	777	110.492	24.449	15.368	1.00	45.72
ATOM	4322	C11	PC	A	777	118.509	32.389	17.081	1.00	49.62
ATOM	4323	C12	PC	A	777	117.647	31.121	17.072	1.00	45.91
ATOM	4324	C13	PC	A	777	116.542	31.091	16.014	1.00	42.05
ATOM	4325	C14	PC	A	777	115.753	32.392	15.973	1.00	37.88
ATOM	4326	C15	PC	A	777	114.269	32.149	16.004	1.00	39.34
ATOM	4327	C16	PC	A	777	113.573	32.877	14.874	1.00	39.38
ATOM	4328	C17	PC	A	777	112.066	32.688	14.951	1.00	43.09
ATOM	4329	C18	PC	A	777	111.446	32.535	13.566	1.00	45.42
ATOM	4330	C19	PC	A	777	111.500	31.093	13.082	1.00	47.16
ATOM	4331	C20	PC	A	777	110.158	30.413	13.236	1.00	46.62
ATOM	4332	C21	PC	A	777	109.917	30.004	14.673	1.00	46.65
ATOM	4333	C22	PC	A	777	108.444	29.836	14.942	1.00	46.97
ATOM	4334	C23	PC	A	777	107.922	30.916	15.868	1.00	47.30
ATOM	4335	C24	PC	A	777	106.409	30.835	16.001	1.00	50.05
ATOM	4336	C25	PC	A	777	105.996	29.898	17.121	1.00	50.59
ATOM	4337	C26	PC	A	777	105.783	28.490	16.612	1.00	53.56
ATOM	4338	C27	PC	A	777	106.972	27.593	16.941	1.00	56.03
ATOM	4339	C28	PC	A	777	107.348	26.625	15.831	1.00	55.75
ATOM	4340	O11	PC	A	777	118.194	33.427	16.467	1.00	52.98
ATOM	4341	O31	PC	A	777	123.576	28.862	17.906	1.00	56.48
ATOM	4342	O2	PC	A	777	122.068	30.020	19.350	1.00	61.36
ATOM	4343	O3	PC	A	777	119.731	32.307	17.866	1.00	53.04
ATOM	4344	O1P	PC	A	777	121.661	35.196	20.857	1.00	89.42
ATOM	4345	O2P	PC	A	777	120.059	33.339	21.280	1.00	90.46
ATOM	4346	O3P	PC	A	777	122.419	32.815	20.622	1.00	84.15
ATOM	4347	O4P	PC	A	777	121.916	33.769	22.889	1.00	91.71
ATOM	4348	N	PC	A	777	125.571	34.153	23.607	1.00	99.82
ATOM	4349	P	PC	A	777	121.516	33.779	21.409	1.00	89.00

SUBSTITUTE SHEET (RULE 26)

ATOM	4350	C1	PC	A	778	87.797	32.791	33.686	1.00	88.29
ATOM	4351	C2	PC	A	778	86.274	32.868	33.502	1.00	83.64
ATOM	4352	C3	PC	A	778	85.739	31.590	32.830	1.00	80 89
ATOM	4353	C31	PC	A	778	84.282	33.619	34.787	1.00	..37
ATOM	4354	C32	PC	A	778	83.704	33.859	33.391	1.00	70.52
ATOM	4355	C33	PC	A	778	82.344	33.215	33.178	1.00	63.44
ATOM	4356	C34	PC	A	778	81.311	34.250	32.803	1.00	56.98
ATOM	4357	C35	PC	A	778	80.231	34.364	33.854	1.00	51.89
ATOM	4358	C36	PC	A	778	79.088	33.400	33.593	1.00	48.39
ATOM	4359	C37	PC	A	778	78.611	33.453	32.155	1.00	47.51
ATOM	4360	C38	PC	A	778	77.593	32.352	31.868	1.00	47.46
ATOM	4361	C39	PC	A	778	78.231	31.153	31.171	1.00	45.28
ATOM	4362	C40	PC	A	778	78.154	31.261	29.654	1.00	43.25
ATOM	4363	C41	PC	A	778	79.381	31.957	29.099	1.00	40.88
ATOM	4364	C42	PC	A	778	79.324	32.082	27.589	1.00	42.02
ATOM	4365	C43	PC	A	778	78.064	32.803	27.130	1.00	43.52
ATOM	4366	C44	PC	A	778	77.971	34.223	27.684	1.00	42.21
ATOM	4367	C45	PC	A	778	76.563	34.546	28.171	1.00	42.30
ATOM	4368	C46	PC	A	778	75.523	34.335	27.077	1.00	42.97
ATOM	4369	C47	PC	A	778	74.121	34.185	27.662	1.00	42.80
ATOM	4370	C48	PC	A	778	73.131	33.504	26.727	1.00	43.31
ATOM	4371	C11	PC	A	778	86.101	31.542	30.412	1.00	71.27
ATOM	4372	C12	PC	A	778	84.804	32.359	30.441	1.00	66.82
ATOM	4373	C13	PC	A	778	83.700	31.845	29.548	1.00	59.12
ATOM	4374	C14	PC	A	778	83.836	32.380	28.141	1.00	55.92
ATOM	4375	C15	PC	A	778	82.896	31.671	27.184	1.00	53.76
ATOM	4376	C16	PC	A	778	82.613	30.248	27.633	1.00	52.97
ATOM	4377	C17	PC	A	778	83.562	29.250	26.990	1.00	50.51
ATOM	4378	C18	PC	A	778	84.990	29.415	27.480	1.00	47.60
ATOM	4379	C19	PC	A	778	85.860	30.046	26.408	1.00	47.69
ATOM	4380	C20	PC	A	778	86.359	29.011	25.411	1.00	44.90
ATOM	4381	C21	PC	A	778	85.271	28.598	24.439	1.00	44.44
ATOM	4382	C22	PC	A	778	85.574	29.064	23.038	1.00	44.15

ATOM	4383	C23	PC	A	778	86.167	30.453	23.044	1.00 43.99
ATOM	4384	C24	PC	A	778	87.670	30.411	22.853	1.00 42.63
ATOM	4385	C25	PC	A	778	88.068	31.161	21.599	1.00 43.28
ATOM	4386	C26	PC	A	778	87.733	32.642	21.693	1.00 41.66
ATOM	4387	C27	PC	A	778	88.852	33.492	21.119	1.00 40.33
ATOM	4388	C28	PC	A	778	90.094	33.503	21.969	1.00 37.09
ATOM	4389	O11	PC	A	778	86.692	31.253	29.343	1.00 72.85
ATOM	4390	O31	PC	A	778	83.619	33.857	35.833	1.00 78.26
ATOM	4391	O2	PC	A	778	85.652	33.065	34.823	1.00 81.22
ATOM	4392	O3	PC	A	778	86.615	31.154	31.736	1.00 75.71
ATOM	4393	O1P	PC	A	778	89.401	31.823	36.960	1.00100.00
ATOM	4394	O2P	PC	A	778	89.563	33.853	35.511	1.00100.00
ATOM	4395	O3P	PC	A	778	88.125	31.917	34.809	1.00 96.24
ATOM	4396	O4P	PC	A	778	87.424	33.342	36.757	1.00100.00
ATOM	4397	P	PC	A	778	88.628	32.739	36.008	1.00100.00
ATOM	4398	OH2	HOH	A	901	116.815	15.747	16.799	1.00 43.90
ATOM	4401	OH2	HOH	A	902	107.439	22.033	22.778	1.00 44.99
ATOM	4404	OH2	HOH	A	903	115.201	26.524	27.768	1.00 47.84
ATOM	4407	OH2	HOH	A	904	83.653	23.737	13.286	1.00 22.80
ATOM	4410	OH2	HOH	A	905	76.576	23.779	22.886	1.00 55.25
ATOM	4413	OH2	HOH	A	906	101.110	43.595	19.882	1.00 44.52
ATOM	4416	OH2	HOH	A	907	80.990	19.920	23.229	1.00 48.61
ATOM	4419	OH2	HOH	A	908	141.374	35.733	18.039	1.00 56.87
ATOM	4422	OH2	HOH	A	909	81.958	22.677	23.953	1.00 61.10
ATOM	4425	OH2	HOH	A	910	152.059	36.697	-0.688	1.00 62.06
ATOM	4428	OH2	HOH	A	911	139.649	24.807	2.271	1.00 53.67
ATOM	4431	OH2	HOH	A	912	124.594	31.177	0.772	1.00 55.59
ATOM	4434	OH2	HOH	A	913	121.471	25.892	1.624	1.00 38.62
ATOM	4437	OH2	HOH	A	914	114.402	25.412	0.380	1.00 31.16
ATOM	4440	OH2	HOH	A	915	147.939	35.177	-2.062	1.00 45.61
ATOM	4443	OH2	HOH	A	916	74.995	34.193	14.634	1.00 73.76
ATOM	4446	OH2	HOH	A	917	105.633	17.580	14.444	1.00 37.72
ATOM	4449	OH2	HOH	A	918	71.679	28.574	37.701	1.00 51.80
ATOM	4452	OH2	HOH	A	919	104.762	14.189	10.052	1.00 57.21

ATOM	4455	OH2	HOH A	920	80.378	28.515	41.681	1.00 81.97
ATOM	4458	OH2	HOH A	921	80.215	25.918	35.227	1.00 29.12
ATOM	4461	OH2	HOH A	922	79.054	35.414	40.975	1.00 41.95
ATOM	4464	OH2	HOH A	923	65.692	27.690	51.372	1.00 65.22
ATOM	4467	OH2	HOH A	924	88.914	24.630	4.689	1.00 48.96
ATOM	4470	OH2	HOH A	925	100.082	22.695	34.405	1.00 48.58
ATOM	4473	OH2	HOH A	926	76.929	19.455	31.644	1.00 86.93
ATOM	4476	OH2	HOH A	927	171.524	31.723	13.880	1.00 59.94
ATOM	4479	OH2	HOH A	928	108.006	35.100	24.514	1.00 49.31
ATOM	4482	OH2	HOH A	929	141.049	21.649	5.587	1.00 42.12
ATOM	4485	OH2	HOH A	930	110.883	40.970	11.363	1.00 35.61
ATOM	4488	OH2	HOH A	931	74.360	34.525	47.158	1.00 75.14
ATOM	4491	OH2	HOH A	932	68.751	40.894	44.809	1.00 43.22
ATOM	4494	OH2	HOH A	933	59.758	29.313	23.460	1.00 61.69
ATOM	4497	OH2	HOH A	934	95.173	16.341	20.293	1.00 48.05
ATOM	4500	OH2	HOH A	935	111.623	41.720	8.640	1.00 53.02
ATOM	4503	OH2	HOH A	936	105.604	16.201	11.554	1.00 71.57
ATOM	4506	OH2	HOH A	937	97.160	30.542	3.465	1.00 58.62
ATOM	4509	OH2	HOH A	938	108.492	10.703	6.225	1.00 76.16
ATOM	4512	OH2	HOH A	939	135.408	44.678	13.765	1.00 61.58
ATOM	4515	OH2	HOH A	940	91.469	31.723	41.685	1.00 41.59
ATOM	4518	OH2	HOH A	941	164.580	32.799	18.975	1.00 48.97
ATOM	4521	OH2	HOH A	942	157.888	29.985	20.509	1.00 63.61
ATOM	4524	OH2	HOH A	943	121.776	21.112	25.392	1.00 61.93
ATOM	4527	OH2	HOH A	944	96.503	38.299	34.009	1.00 64.71
ATOM	4530	OH2	HOH A	945	96.403	17.036	28.115	1.00 76.51
ATOM	4533	OH2	HOH A	946	88.114	18.204	31.407	1.00 52.33
ATOM	4536	OH2	HOH A	947	81.217	23.098	12.608	1.00 35.93
ATOM	4539	OH2	HOH A	948	126.713	24.917	0.514	1.00 82.50
TER								
END								

Atom Type	Residue	#	X	Y	Z	OCC	B

SUBSTITUTE SHEET (RULE 26)

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REMARK   3
REMARK   3 REFINEMENT.
REMARK   3   PROGRAM     : X-PLOR(online) 3.843
REMARK   3   AUTHORS     : BRUNGER
REMARK   3
REMARK   3  DATA USED IN REFINEMENT.
REMARK   3   RESOLUTION RANGE HIGH (ANGSTROMS) : 2.40
REMARK   3   RESOLUTION RANGE LOW  (ANGSTROMS) :50.00
REMARK   3   DATA CUTOFF            (SIGMA(F)) : 0.0
REMARK   3   DATA CUTOFF HIGH         (ABS(F)) :   100000.00
REMARK   3   DATA CUTOFF LOW          (ABS(F)) :     0.010000
REMARK   3   COMPLETENESS (WORKING+TEST )   (%) : 92.7
REMARK   3   NUMBER OF REFLECTIONS              : 18908
REMARK   3
REMARK   3  FIT TO DATA USED IN REFINEMENT.
REMARK   3   CROSS-VALIDATION METHOD          : THROUGHOUT
REMARK   3   FREE R VALUE TEST SET SELECTION  : RANDOM
REMARK   3   R VALUE            (WORKING SET) : 0.225
REMARK   3   FREE R VALUE                     : 0.295
REMARK   3   FREE R VALUE TEST SET SIZE   (%) : 10.2
REMARK   3   FREE R VALUE TEST SET COUNT      :  1926
REMARK   3   ESTIMATED ERROR OF FREE R VALUE  : 0.007
REMARK   3
REMARK   3  FIT IN THE HIGHEST RESOLUTION BIN.
REMARK   3   TOTAL NUMBER OF BINS USED           :   6
REMARK   3   BIN RESOLUTION RANGE HIGH       (A) : 2.40
REMARK   3   BIN RESOLUTION RANGE LOW        (A) : 2.55
REMARK   3   BIN COMPLETENESS (WORKING+TEST) (%) : 94.1
REMARK   3   REFLECTIONS IN BIN    (WORKING SET) :  2875
REMARK   3   BIN R VALUE           (WORKING SET) : 0.368
REMARK   3   BIN FREE R VALUE                    : 0.455
REMARK   3   BIN FREE R VALUE TEST SET SIZE  (%) :  8.7
REMARK   3   BIN FREE R VALUE TEST SET COUNT     :   275
REMARK   3   ESTIMATED ERROR OF BIN FREE R VALUE : 0.027
REMARK   3
REMARK   3  NUMBER OF NON-HYDROGEN ATOMS USED IN REFINEMENT.
REMARK   3   PROTEIN ATOMS            : 3531
REMARK   3   NUCLEIC ACID ATOMS       :    0
REMARK   3   HETEROGEN ATOMS          :  102
REMARK   3   SOLVENT ATOMS            :   48
REMARK   3
REMARK   3  B VALUES.
REMARK   3   FROM WILSON PLOT           (A**2) : 45.0
REMARK   3   MEAN B VALUE      (OVERALL, A**2) : 45.0
REMARK   3   OVERALL ANISOTROPIC B VALUE.
REMARK   3    B11 (A**2) :-11.35
REMARK   3    B22 (A**2) :  6.33
REMARK   3    B33 (A**2) :  5.02
REMARK   3    B12 (A**2) :  0.00
REMARK   3    B13 (A**2) :  7.70
REMARK   3    B23 (A**2) :  0.00
REMARK   3
REMARK   3  ESTIMATED COORDINATE ERROR.
REMARK   3   ESD FROM LUZZATI PLOT        (A) : 0.34
REMARK   3   ESD FROM SIGMAA              (A) : 0.47
REMARK   3   LOW RESOLUTION CUTOFF        (A) : 5.00
REMARK   3
REMARK   3  CROSS-VALIDATED ESTIMATED COORDINATE ERROR.
REMARK   3   ESD FROM C-V LUZZATI PLOT    (A) : 0.45
REMARK   3   ESD FROM C-V SIGMAA          (A) : 0.46
REMARK   3
REMARK   3  RMS DEVIATIONS FROM IDEAL VALUES.
REMARK   3   BOND LENGTHS                 (A) : 0.007
REMARK   3   BOND ANGLES            (DEGREES) : 1.4
REMARK   3   DIHEDRAL ANGLES        (DEGREES) : 26.1
REMARK   3   IMPROPER ANGLES        (DEGREES) : 1.24
REMARK   3
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0094694 - 980758

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REMARK   3  ISOTROPIC THERMAL MODEL : RESTRAINED
REMARK   3
REMARK   3  ISOTROPIC THERMAL FACTOR RESTRAINTS.      RMS     SIGMA
REMARK   3   MAIN-CHAIN BOND              (A**2) :  1.77 ;  1.50
REMARK   3   MAIN-CHAIN ANGLE             (A**2) :  3.00 ;  2.00
REMARK   3   SIDE-CHAIN BOND              (A**2) :  2.81 ;  2.00
REMARK   3   SIDE-CHAIN ANGLE             (A**2) :  4.53 ;  2.50
REMARK   3
REMARK   3  NCS MODEL                 : NONE
REMARK   3
REMARK   3  NCS RESTRAINTS.                          RMS   SIGMA/WEIGHT
REMARK   3   GROUP 1  POSITIONAL               (A) : NULL  ; NULL
REMARK   3   GROUP 1  B-FACTOR            (A**2) : NULL  ; NULL
REMARK   3
REMARK   3  PARAMETER FILE 1  : parhcsdx.pro
REMARK   3  PARAMETER FILE 2  : param11.wat
REMARK   3  TOPOLOGY FILE 1   : tophcsdx.pro
REMARK   3  TOPOLOGY FILE 2   : toph11.wat
REMARK   3
REMARK   3  OTHER REFINEMENT REMARKS: BULK SOLVENT MODEL USED
SEQRES   1 A  507  VAL ASN PRO GLY VAL VAL VAL ARG ILE SER GLN LYS GLY
SEQRES   2 A  507  LEU ASP TYR ALA SER GLN GLN GLY THR ALA ALA LEU GLN
SEQRES   3 A  507  LYS GLU LEU LYS ARG ILE LYS ILE PRO ASP TYR SER ASP
SEQRES   4 A  507  SER PHE LYS ILE LYS HIS LEU GLY LYS GLY HIS TYR SER
SEQRES   5 A  507  PHE TYR SER MET ASP ILE ARG GLU PHE GLN LEU PRO SER
SEQRES   6 A  507  SER GLN ILE SER MET VAL PRO ASN VAL GLY LEU LYS PHE
SEQRES   7 A  507  SER ILE SER ASN ALA ASN ILE LYS ILE SER GLY LYS TRP
SEQRES   8 A  507  LYS ALA GLN LYS ARG PHE LEU LYS MET SER GLY ASN PHE
SEQRES   9 A  507  ASP LEU SER ILE GLU GLY MET SER ILE SER ALA ASP LEU
SEQRES  10 A  507  LYS LEU GLY SER ASN PRO THR SER GLY LYS PRO THR ILE
SEQRES  11 A  507  THR CYS SER SER CYS SER SER HIS ILE ASN SER VAL HIS
SEQRES  12 A  507  VAL HIS ILE SER ALA ALA SER VAL GLY TRP LEU ILE GLN
SEQRES  13 A  507  LEU PHE HIS LYS LYS ILE GLU SER ALA LEU ARG ASN LYS
SEQRES  14 A  507  MET ASN SER GLN VAL CYS GLU LYS VAL THR ASN SER VAL
SEQRES  15 A  507  SER SER GLU LEU GLN PRO TYR PHE GLN THR LEU PRO VAL
SEQRES  16 A  507  MET THR LYS ILE ASP SER VAL ALA GLY ILE ASN TYR GLY
SEQRES  17 A  507  LEU VAL ALA PRO PRO ALA THR THR ALA GLU THR LEU ASP
SEQRES  18 A  507  VAL GLN MET LYS GLY GLU PHE TYR SER GLU ALA ALA ALA
SEQRES  19 A  507  ALA PRO PRO PRO PHE ALA PRO PRO VAL MET GLU PHE PRO
SEQRES  20 A  507  ALA ALA ALA ASP ARG MET VAL TYR LEU GLY LEU SER ASP
SEQRES  21 A  507  TYR PHE PHE ASN THR ALA GLY LEU VAL TYR GLN GLU ALA
SEQRES  22 A  507  GLY VAL LEU LYS MET THR LEU ARG ASP ASP MET ILE PRO
SEQRES  23 A  507  LYS GLU SER ALA PHE ARG LEU THR THR SER PHE PHE GLY
SEQRES  24 A  507  THR PHE LEU PRO GLU VAL ALA LYS LYS PHE PRO ASN MET
SEQRES  25 A  507  LYS ILE GLN ILE HIS VAL SER ALA SER THR PRO PRO HIS
SEQRES  26 A  507  LEU SER VAL GLN PRO THR GLY LEU THR PHE TYR PRO ALA
SEQRES  27 A  507  VAL ASP VAL GLN ALA PHE ALA VAL LEU PRO ASN SER ALA
SEQRES  28 A  507  LEU ALA SER LEU PHE LEU ILE GLY MET HIS THR THR GLY
SEQRES  29 A  507  SER MET GLU VAL SER ALA GLU SER ASN ARG LEU VAL GLY
SEQRES  30 A  507  GLU LEU LYS LEU ASP ARG LEU LEU LEU GLU LEU LYS HIS
SEQRES  31 A  507  SER ASN ILE GLY PRO PHE PRO VAL GLU LEU LEU GLN ASP
SEQRES  32 A  507  ILE MET ASN TYR ILE VAL PRO ILE LEU VAL LEU PRO ARG
SEQRES  33 A  507  VAL ASN GLU LYS LEU GLN LYS GLY PHE PRO LEU PRO THR
SEQRES  34 A  507  PRO ALA ARG VAL GLN LEU TYR ASN VAL VAL LEU GLN PRO
SEQRES  35 A  507  HIS GLN ASN PHE LEU LEU PHE GLY ALA ASP VAL VAL TYR
SEQRES  36 A  507  LYS PC PC HOH HOH HOH HOH HOH HOH HOH HOH HOH HOH
SEQRES  37 A  507  HOH HOH HOH HOH HOH HOH HOH HOH HOH HOH HOH HOH HOH
SEQRES  38 A  507  HOH HOH HOH HOH HOH HOH HOH HOH HOH HOH HOH HOH HOH
SEQRES  39 A  507  HOH HOH HOH HOH HOH HOH HOH HOH HOH HOH HOH HOH HOH
SSBOND   1 CYS A  135    CYS A  175
CRYST1  185.600   33.000   85.200  90.00 101.60  90.00 C 2              4
ORIGX1      1.000000  0.000000  0.000000        0.00000
ORIGX2      0.000000  1.000000  0.000000        0.00000
ORIGX3      0.000000  0.000000  1.000000        0.00000
SCALE1      0.005388  0.000000  0.001106        0.00000
SCALE2      0.000000  0.030303  0.000000        0.00000
SCALE3      0.000000  0.000000  0.011982        0.00000
```

09814455 - 071900

The following abbreviations are used in Table 4 in accordance with the format and usage established by the Protein Data Bank ("PDB"), Brookhaven National Laboratory, Brookhaven, N.Y. These coordinates are on deposit with the PDB, ID code 1bp1. Atomic coordinates of a BPI protein as described herein appear at Table 4 (pages 62-171 herein) and refinement statistics also appear at the end of Table 4 (pages 172-173 herein). Table 4 corresponds to Figure 6 (Figs. 6.1-6.112) in United States patent application serial no. 08/879,565, filed June 20, 1997.

"Atom type" refers to the element whose coordinates are measured. The first letter in the column defines the element.

"Residue" refers to the amino acid in the BPI protein sequence, using the standard three letter abbreviations known in the art.

"#" refers to the residue number.

"X, Y, Z" crystallographically define the atomic position, in three-dimensional space, of the element measured.

"OCC" is the occupancy value.

"B" is a thermal factor that measures movement of the atom around its atomic center.

10. **Organomimetics**

Molecular modelling of BPI as described herein is useful for the preparation of organomimetics such as "surface" mimetics. As one example, organomimetics are prepared based on "tip" mimetics in which the three-dimensional coordinates of the tip, as described above, are used to create a "surface" (or complementary pocket) into which a computer program builds an organic molecule with similar characteristics.

Numerous modifications and variations in the practice of the invention are expected to occur to those skilled in the art upon consideration of the foregoing description and the presently preferred embodiments thereof. Consequently, the scope of the present invention is to be defined by the appended claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: XOMA Corporation; (Beamer, Lesa J., Carroll, Stephen F., Eisenberg, David, U.S. only)

(ii) TITLE OF INVENTION: Bactericidal/Permeability-Increasing Protein: Crystallization, X-Ray Diffraction, Three-Dimensional Structure Determination, Rational Drug Design and Molecular Modeling of Related Proteins

(iii) NUMBER OF SEQUENCES: 2

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: McAndrews, Held & Malloy
(B) STREET: 500 West Madison, 34th Floor
(C) CITY: Chicago
(D) STATE: Illinois
(E) COUNTRY: United States of America
(F) ZIP: 60661

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: U.S. Serial No. 08/879,565
(B) FILING DATE: June 20, 1997
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: McNicholas, Janet M.
(B) REGISTRATION NUMBER: 32,918
(C) REFERENCE/DOCKET NUMBER: 11034WO01/100-248.PCT

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 312/707-8889
(B) TELEFAX: 312/707-9155
(C) TELEX:

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1813 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 31..1491

(ix) FEATURE:
(A) NAME/KEY: mat_peptide

(B) LOCATION: 124..1491

(ix) FEATURE:
(A) NAME/KEY: misc_feature

(D) OTHER INFORMATION: "rBPI"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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CAGGCCTTGA GGTTTTGGCA GCTCTGGAGG ATG AGA GAG AAC ATG GCC AGG GGC        54
                                 Met Arg Glu Asn Met Ala Arg Gly
                                 -31 -30                 -25

CCT TGC AAC GCG CCG AGA TGG GTG TCC CTG ATG GTG CTC GTC GCC ATA        102
Pro Cys Asn Ala Pro Arg Trp Val Ser Leu Met Val Leu Val Ala Ile
            -20                 -15                 -10

GGC ACC GCC GTG ACA GCG GCC GTC AAC CCT GGC GTC GTG GTC AGG ATC        150
Gly Thr Ala Val Thr Ala Ala Val Asn Pro Gly Val Val Val Arg Ile
         -5                  1                   5

TCC CAG AAG GGC CTG GAC TAC GCC AGC CAG CAG GGG ACG GCC GCT CTG        198
Ser Gln Lys Gly Leu Asp Tyr Ala Ser Gln Gln Gly Thr Ala Ala Leu
 10                  15                  20                  25

CAG AAG GAG CTG AAG AGG ATC AAG ATT CCT GAC TAC TCA GAC AGC TTT        246
Gln Lys Glu Leu Lys Arg Ile Lys Ile Pro Asp Tyr Ser Asp Ser Phe
                 30                  35                  40

AAG ATC AAG CAT CTT GGG AAG GGG CAT TAT AGC TTC TAC AGC ATG GAC        294
Lys Ile Lys His Leu Gly Lys Gly His Tyr Ser Phe Tyr Ser Met Asp
             45                  50                  55

ATC CGT GAA TTC CAG CTT CCC AGT TCC CAG ATA AGC ATG GTG CCC AAT        342
Ile Arg Glu Phe Gln Leu Pro Ser Ser Gln Ile Ser Met Val Pro Asn
         60                  65                  70

GTG GGC CTT AAG TTC TCC ATC AGC AAC GCC AAT ATC AAG ATC AGC GGG        390
Val Gly Leu Lys Phe Ser Ile Ser Asn Ala Asn Ile Lys Ile Ser Gly
     75                  80                  85

AAA TGG AAG GCA CAA AAG AGA TTC TTA AAA ATG AGC GGC AAT TTT GAC        438
Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys Met Ser Gly Asn Phe Asp
 90                  95                  100                 105

CTG AGC ATA GAA GGC ATG TCC ATT TCG GCT GAT CTG AAG CTG GGC AGT        486
Leu Ser Ile Glu Gly Met Ser Ile Ser Ala Asp Leu Lys Leu Gly Ser
                110                 115                 120

AAC CCC ACG TCA GGC AAG CCC ACC ATC ACC TGC TCC AGC TGC AGC AGC        534
Asn Pro Thr Ser Gly Lys Pro Thr Ile Thr Cys Ser Ser Cys Ser Ser
            125                 130                 135

CAC ATC AAC AGT GTC CAC GTG CAC ATC TCA AAG AGC AAA GTC GGG TGG        582
His Ile Asn Ser Val His Val His Ile Ser Lys Ser Lys Val Gly Trp
        140                 145                 150

CTG ATC CAA CTC TTC CAC AAA AAA ATT GAG TCT GCG CTT CGA AAC AAG        630
Leu Ile Gln Leu Phe His Lys Lys Ile Glu Ser Ala Leu Arg Asn Lys
    155                 160                 165

ATG AAC AGC CAG GTC TGC GAG AAA GTG ACC AAT TCT GTA TCC TCC AAG        678
Met Asn Ser Gln Val Cys Glu Lys Val Thr Asn Ser Val Ser Ser Lys
170                 175                 180                 185

CTG CAA CCT TAT TTC CAG ACT CTG CCA GTA ATG ACC AAA ATA GAT TCT        726
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Leu Gln Pro Tyr Phe Gln Thr Leu Pro Val Met Thr Lys Ile Asp Ser
                190                 195                 200

GTG GCT GGA ATC AAC TAT GGT CTG GTG GCA CCT CCA GCA ACC ACG GCT      774
Val Ala Gly Ile Asn Tyr Gly Leu Val Ala Pro Pro Ala Thr Thr Ala
            205                 210                 215

GAG ACC CTG GAT GTA CAG ATG AAG GGG GAG TTT TAC AGT GAG AAC CAC      822
Glu Thr Leu Asp Val Gln Met Lys Gly Glu Phe Tyr Ser Glu Asn His
        220                 225                 230

CAC AAT CCA CCT CCC TTT GCT CCA CCA GTG ATG GAG TTT CCC GCT GCC      870
His Asn Pro Pro Pro Phe Ala Pro Pro Val Met Glu Phe Pro Ala Ala
    235                 240                 245

CAT GAC CGC ATG GTA TAC CTG GGC CTC TCA GAC TAC TTC TTC AAC ACA      918
His Asp Arg Met Val Tyr Leu Gly Leu Ser Asp Tyr Phe Phe Asn Thr
250                 255                 260                 265

GCC GGG CTT GTA TAC CAA GAG GCT GGG GTC TTG AAG ATG ACC CTT AGA      966
Ala Gly Leu Val Tyr Gln Glu Ala Gly Val Leu Lys Met Thr Leu Arg
                270                 275                 280

GAT GAC ATG ATT CCA AAG GAG TCC AAA TTT CGA CTG ACA ACC AAG TTC     1014
Asp Asp Met Ile Pro Lys Glu Ser Lys Phe Arg Leu Thr Thr Lys Phe
            285                 290                 295

TTT GGA ACC TTC CTA CCT GAG GTG GCC AAG AAG TTT CCC AAC ATG AAG     1062
Phe Gly Thr Phe Leu Pro Glu Val Ala Lys Lys Phe Pro Asn Met Lys
        300                 305                 310

ATA CAG ATC CAT GTC TCA GCC TCC ACC CCG CCA CAC CTG TCT GTG CAG     1110
Ile Gln Ile His Val Ser Ala Ser Thr Pro Pro His Leu Ser Val Gln
    315                 320                 325

CCC ACC GGC CTT ACC TTC TAC CCT GCC GTG GAT GTC CAG GCC TTT GCC     1158
Pro Thr Gly Leu Thr Phe Tyr Pro Ala Val Asp Val Gln Ala Phe Ala
330                 335                 340                 345

GTC CTC CCC AAC TCC TCC CTG GCT TCC CTC TTC CTG ATT GGC ATG CAC     1206
Val Leu Pro Asn Ser Ser Leu Ala Ser Leu Phe Leu Ile Gly Met His
                350                 355                 360

ACA ACT GGT TCC ATG GAG GTC AGC GCC GAG TCC AAC AGG CTT GTT GGA     1254
Thr Thr Gly Ser Met Glu Val Ser Ala Glu Ser Asn Arg Leu Val Gly
            365                 370                 375

GAG CTC AAG CTG GAT AGG CTG CTC CTG GAA CTG AAG CAC TCA AAT ATT     1302
Glu Leu Lys Leu Asp Arg Leu Leu Leu Glu Leu Lys His Ser Asn Ile
        380                 385                 390

GGC CCC TTC CCG GTT GAA TTG CTG CAG GAT ATC ATG AAC TAC ATT GTA     1350
Gly Pro Phe Pro Val Glu Leu Leu Gln Asp Ile Met Asn Tyr Ile Val
    395                 400                 405

CCC ATT CTT GTG CTG CCC AGG GTT AAC GAG AAA CTA CAG AAA GGC TTC     1398
Pro Ile Leu Val Leu Pro Arg Val Asn Glu Lys Leu Gln Lys Gly Phe
410                 415                 420                 425

CCT CTC CCG ACG CCG GCC AGA GTC CAG CTC TAC AAC GTA GTG CTT CAG     1446
Pro Leu Pro Thr Pro Ala Arg Val Gln Leu Tyr Asn Val Val Leu Gln
                430                 435                 440

CCT CAC CAG AAC TTC CTG CTG TTC GGT GCA GAC GTT GTC TAT AAA         1491
Pro His Gln Asn Phe Leu Leu Phe Gly Ala Asp Val Val Tyr Lys
            445                 450                 455
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TGAAGGCACC AGGGGTGCCG GGGGCTGTCA GCCGCACCTG TTCCTGATGG GCTGTGGGGC 1551

ACCGGCTGCC TTTCCCCAGG GAATCCTCTC CAGATCTTAA CCAAGAGCCC CTTGCAAACT 1611

TCTTCGACTC AGATTCAGAA ATGATCTAAA CACGAGGAAA CATTATTCAT TGGAAAAGTG 1671

CATGGTGTGT ATTTTAGGGA TTATGAGCTT CTTTCAAGGG CTAAGGCTGC AGAGATATTT 1731

CCTCCAGGAA TCGTGTTTCA ATTGTAACCA AGAAATTTCC ATTTGTGCTT CATGAAAAAA 1791

AACTTCTGGT TTTTTTCATG TG 1813

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 487 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Arg Glu Asn Met Ala Arg Gly Pro Cys Asn Ala Pro Arg Trp Val
-31 -30 -25 -20

Ser Leu Met Val Leu Val Ala Ile Gly Thr Ala Val Thr Ala Ala Val
-15 -10 -5 1

Asn Pro Gly Val Val Val Arg Ile Ser Gln Lys Gly Leu Asp Tyr Ala
5 10 15

Ser Gln Gln Gly Thr Ala Ala Leu Gln Lys Glu Leu Lys Arg Ile Lys
20 25 30

Ile Pro Asp Tyr Ser Asp Ser Phe Lys Ile Lys His Leu Gly Lys Gly
35 40 45

His Tyr Ser Phe Tyr Ser Met Asp Ile Arg Glu Phe Gln Leu Pro Ser
50 55 60 65

Ser Gln Ile Ser Met Val Pro Asn Val Gly Leu Lys Phe Ser Ile Ser
70 75 80

Asn Ala Asn Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg Phe
85 90 95

Leu Lys Met Ser Gly Asn Phe Asp Leu Ser Ile Glu Gly Met Ser Ile
100 105 110

Ser Ala Asp Leu Lys Leu Gly Ser Asn Pro Thr Ser Gly Lys Pro Thr
115 120 125

Ile Thr Cys Ser Ser Cys Ser Ser His Ile Asn Ser Val His Val His
130 135 140 145

Ile Ser Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Phe His Lys Lys
150 155 160

Ile Glu Ser Ala Leu Arg Asn Lys Met Asn Ser Gln Val Cys Glu Lys
165 170 175

Val Thr Asn Ser Val Ser Ser Lys Leu Gln Pro Tyr Phe Gln Thr Leu
180 185 190

Pro Val Met Thr Lys Ile Asp Ser Val Ala Gly Ile Asn Tyr Gly Leu

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195 200 205

Val Ala Pro Pro Ala Thr Thr Ala Glu Thr Leu Asp Val Gln Met Lys
210 215 220 225

Gly Glu Phe Tyr Ser Glu Asn His His Asn Pro Pro Pro Phe Ala Pro
230 235 240

Pro Val Met Glu Phe Pro Ala Ala His Asp Arg Met Val Tyr Leu Gly
245 250 255

Leu Ser Asp Tyr Phe Phe Asn Thr Ala Gly Leu Val Tyr Gln Glu Ala
260 265 270

Gly Val Leu Lys Met Thr Leu Arg Asp Asp Met Ile Pro Lys Glu Ser
275 280 285

Lys Phe Arg Leu Thr Thr Lys Phe Phe Gly Thr Phe Leu Pro Glu Val
290 295 300 305

Ala Lys Lys Phe Pro Asn Met Lys Ile Gln Ile His Val Ser Ala Ser
310 315 320

Thr Pro Pro His Leu Ser Val Gln Pro Thr Gly Leu Thr Phe Tyr Pro
325 330 335

Ala Val Asp Val Gln Ala Phe Ala Val Leu Pro Asn Ser Ser Leu Ala
340 345 350

Ser Leu Phe Leu Ile Gly Met His Thr Thr Gly Ser Met Glu Val Ser
355 360 365

Ala Glu Ser Asn Arg Leu Val Gly Glu Leu Lys Leu Asp Arg Leu Leu
370 375 380 385

Leu Glu Leu Lys His Ser Asn Ile Gly Pro Phe Pro Val Glu Leu Leu
390 395 400

Gln Asp Ile Met Asn Tyr Ile Val Pro Ile Leu Val Leu Pro Arg Val
405 410 415

Asn Glu Lys Leu Gln Lys Gly Phe Pro Leu Pro Thr Pro Ala Arg Val
420 425 430

Gln Leu Tyr Asn Val Val Leu Gln Pro His Gln Asn Phe Leu Leu Phe
435 440 445

Gly Ala Asp Val Val Tyr Lys
450 455

SUBSTITUTE SHEET (RULE 26)

09/446415
420 Rec'd PCT/PTO 20 DEC 1999.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Beamer, Lesa J., Carroll, Stephen F., Eisenber, David

(ii) TITLE OF INVENTION: Bactericidal/Permeability-Increasing Protein: Crystallization, X-Ray Diffraction, Three-Dimensional Structure Determination, Rational Drug Design and Molecular Modeling of Related Proteins

(iii) NUMBER OF SEQUENCES: 2

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: McAndrews, Held & Malloy
(B) STREET: 500 West Madison, 34th Floor
(C) CITY: Chicago
(D) STATE: Illinois
(E) COUNTRY: United States of America
(F) ZIP: 60661

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: McNicholas, Janet M.
(B) REGISTRATION NUMBER: 32,918
(C) REFERENCE/DOCKET NUMBER: 11034US01;100-248

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 312/707-8889
(B) TELEFAX: 312/707-9155
(C) TELEX:

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1813 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 31..1491

(ix) FEATURE:
(A) NAME/KEY: mat_peptide
(B) LOCATION: 124..1491

(ix) FEATURE:
(A) NAME/KEY: misc_feature

(D) OTHER INFORMATION: "rBPI"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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CAGGCCTTGA GGTTTTGGCA GCTCTGGAGG ATG AGA GAG AAC ATG GCC AGG GGC        54
                                 Met Arg Glu Asn Met Ala Arg Gly
                                 -31 -30                 -25

CCT TGC AAC GCG CCG AGA TGG GTG TCC CTG ATG GTG CTC GTC GCC ATA       102
Pro Cys Asn Ala Pro Arg Trp Val Ser Leu Met Val Leu Val Ala Ile
        -20                 -15                 -10

GGC ACC GCC GTG ACA GCG GCC GTC AAC CCT GGC GTC GTG GTC AGG ATC       150
Gly Thr Ala Val Thr Ala Ala Val Asn Pro Gly Val Val Val Arg Ile
    -5                  1                   5

TCC CAG AAG GGC CTG GAC TAC GCC AGC CAG CAG GGG ACG GCC GCT CTG       198
Ser Gln Lys Gly Leu Asp Tyr Ala Ser Gln Gln Gly Thr Ala Ala Leu
10                  15                  20                  25

CAG AAG GAG CTG AAG AGG ATC AAG ATT CCT GAC TAC TCA GAC AGC TTT       246
Gln Lys Glu Leu Lys Arg Ile Lys Ile Pro Asp Tyr Ser Asp Ser Phe
            30                  35                  40

AAG ATC AAG CAT CTT GGG AAG GGG CAT TAT AGC TTC TAC AGC ATG GAC       294
Lys Ile Lys His Leu Gly Lys Gly His Tyr Ser Phe Tyr Ser Met Asp
        45                  50                  55

ATC CGT GAA TTC CAG CTT CCC AGT TCC CAG ATA AGC ATG GTG CCC AAT       342
Ile Arg Glu Phe Gln Leu Pro Ser Ser Gln Ile Ser Met Val Pro Asn
    60                  65                  70

GTG GGC CTT AAG TTC TCC ATC AGC AAC GCC AAT ATC AAG ATC AGC GGG       390
Val Gly Leu Lys Phe Ser Ile Ser Asn Ala Asn Ile Lys Ile Ser Gly
75                  80                  85

AAA TGG AAG GCA CAA AAG AGA TTC TTA AAA ATG AGC GGC AAT TTT GAC       438
Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys Met Ser Gly Asn Phe Asp
90                  95                  100                 105

CTG AGC ATA GAA GGC ATG TCC ATT TCG GCT GAT CTG AAG CTG GGC AGT       486
Leu Ser Ile Glu Gly Met Ser Ile Ser Ala Asp Leu Lys Leu Gly Ser
            110                 115                 120
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AAC CCC ACG TCA GGC AAG CCC ACC ATC ACC TGC TCC AGC TGC AGC AGC      534
Asn Pro Thr Ser Gly Lys Pro Thr Ile Thr Cys Ser Ser Cys Ser Ser
            125                 130                 135

CAC ATC AAC AGT GTC CAC GTG CAC ATC TCA AAG AGC AAA GTC GGG TGG      582
His Ile Asn Ser Val His Val His Ile Ser Lys Ser Lys Val Gly Trp
        140                 145                 150

CTG ATC CAA CTC TTC CAC AAA AAA ATT GAG TCT GCG CTT CGA AAC AAG      630
Leu Ile Gln Leu Phe His Lys Lys Ile Glu Ser Ala Leu Arg Asn Lys
    155                 160                 165

ATG AAC AGC CAG GTC TGC GAG AAA GTG ACC AAT TCT GTA TCC TCC AAG      678
Met Asn Ser Gln Val Cys Glu Lys Val Thr Asn Ser Val Ser Ser Lys
170                 175                 180                 185

CTG CAA CCT TAT TTC CAG ACT CTG CCA GTA ATG ACC AAA ATA GAT TCT      726
Leu Gln Pro Tyr Phe Gln Thr Leu Pro Val Met Thr Lys Ile Asp Ser
                190                 195                 200

GTG GCT GGA ATC AAC TAT GGT CTG GTG GCA CCT CCA GCA ACC ACG GCT      774
Val Ala Gly Ile Asn Tyr Gly Leu Val Ala Pro Pro Ala Thr Thr Ala
            205                 210                 215

GAG ACC CTG GAT GTA CAG ATG AAG GGG GAG TTT TAC AGT GAG AAC CAC      822
Glu Thr Leu Asp Val Gln Met Lys Gly Glu Phe Tyr Ser Glu Asn His
        220                 225                 230

CAC AAT CCA CCT CCC TTT GCT CCA CCA GTG ATG GAG TTT CCC GCT GCC      870
His Asn Pro Pro Pro Phe Ala Pro Pro Val Met Glu Phe Pro Ala Ala
    235                 240                 245

CAT GAC CGC ATG GTA TAC CTG GGC CTC TCA GAC TAC TTC TTC AAC ACA      918
His Asp Arg Met Val Tyr Leu Gly Leu Ser Asp Tyr Phe Phe Asn Thr
250                 255                 260                 265

GCC GGG CTT GTA TAC CAA GAG GCT GGG GTC TTG AAG ATG ACC CTT AGA      966
Ala Gly Leu Val Tyr Gln Glu Ala Gly Val Leu Lys Met Thr Leu Arg
                270                 275                 280

GAT GAC ATG ATT CCA AAG GAG TCC AAA TTT CGA CTG ACA ACC AAG TTC     1014
Asp Asp Met Ile Pro Lys Glu Ser Lys Phe Arg Leu Thr Thr Lys Phe
            285                 290                 295

TTT GGA ACC TTC CTA CCT GAG GTG GCC AAG AAG TTT CCC AAC ATG AAG     1062
Phe Gly Thr Phe Leu Pro Glu Val Ala Lys Lys Phe Pro Asn Met Lys
        300                 305                 310

ATA CAG ATC CAT GTC TCA GCC TCC ACC CCG CCA CAC CTG TCT GTG CAG     1110
Ile Gln Ile His Val Ser Ala Ser Thr Pro Pro His Leu Ser Val Gln
    315                 320                 325

CCC ACC GGC CTT ACC TTC TAC CCT GCC GTG GAT GTC CAG GCC TTT GCC     1158
Pro Thr Gly Leu Thr Phe Tyr Pro Ala Val Asp Val Gln Ala Phe Ala
330                 335                 340                 345
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Val Leu Pro Asn Ser Ser Leu Ala Ser Leu Phe Leu Ile Gly Met His
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ACA ACT GGT TCC ATG GAG GTC AGC GCC GAG TCC AAC AGG CTT GTT GGA      1254
Thr Thr Gly Ser Met Glu Val Ser Ala Glu Ser Asn Arg Leu Val Gly
            365                 370                 375

GAG CTC AAG CTG GAT AGG CTG CTC CTG GAA CTG AAG CAC TCA AAT ATT      1302
Glu Leu Lys Leu Asp Arg Leu Leu Leu Glu Leu Lys His Ser Asn Ile
        380                 385                 390

GGC CCC TTC CCG GTT GAA TTG CTG CAG GAT ATC ATG AAC TAC ATT GTA      1350
Gly Pro Phe Pro Val Glu Leu Leu Gln Asp Ile Met Asn Tyr Ile Val
    395                 400                 405

CCC ATT CTT GTG CTG CCC AGG GTT AAC GAG AAA CTA CAG AAA GGC TTC      1398
Pro Ile Leu Val Leu Pro Arg Val Asn Glu Lys Leu Gln Lys Gly Phe
410                 415                 420                 425

CCT CTC CCG ACG CCG GCC AGA GTC CAG CTC TAC AAC GTA GTG CTT CAG      1446
Pro Leu Pro Thr Pro Ala Arg Val Gln Leu Tyr Asn Val Val Leu Gln
                430                 435                 440

CCT CAC CAG AAC TTC CTG CTG TTC GGT GCA GAC GTT GTC TAT AAA          1491
Pro His Gln Asn Phe Leu Leu Phe Gly Ala Asp Val Val Tyr Lys
            445                 450                 455

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ACCGGCTGCC TTTCCCCAGG GAATCCTCTC CAGATCTTAA CCAAGAGCCC CTTGCAAACT    1611

TCTTCGACTC AGATTCAGAA ATGATCTAAA CACGAGGAAA CATTATTCAT TGGAAAAGTG    1671

CATGGTGTGT ATTTTAGGGA TTATGAGCTT CTTTCAAGGG CTAAGGCTGC AGAGATATTT    1731

CCTCCAGGAA TCGTGTTTCA ATTGTAACCA AGAAATTTCC ATTTGTGCTT CATGAAAAAA    1791

AACTTCTGGT TTTTTTCATG TG                                              1813
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 487 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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-15                 -10                 -5                  1
```

0 0 0

Asn Pro Gly Val Val Val Arg Ile Ser Gln Lys Gly Leu Asp Tyr Ala
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Ser Gln Gln Gly Thr Ala Ala Leu Gln Lys Glu Leu Lys Arg Ile Lys
20 25 30

Ile Pro Asp Tyr Ser Asp Ser Phe Lys Ile Lys His Leu Gly Lys Gly
35 40 45

His Tyr Ser Phe Tyr Ser Met Asp Ile Arg Glu Phe Gln Leu Pro Ser
50 55 60 65

Ser Gln Ile Ser Met Val Pro Asn Val Gly Leu Lys Phe Ser Ile Ser
70 75 80

Asn Ala Asn Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg Phe
85 90 95

Leu Lys Met Ser Gly Asn Phe Asp Leu Ser Ile Glu Gly Met Ser Ile
100 105 110

Ser Ala Asp Leu Lys Leu Gly Ser Asn Pro Thr Ser Gly Lys Pro Thr
115 120 125

Ile Thr Cys Ser Ser Cys Ser Ser His Ile Asn Ser Val His Val His
130 135 140 145

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150 155 160

Ile Glu Ser Ala Leu Arg Asn Lys Met Asn Ser Gln Val Cys Glu Lys
165 170 175

Val Thr Asn Ser Val Ser Ser Lys Leu Gln Pro Tyr Phe Gln Thr Leu
180 185 190

Pro Val Met Thr Lys Ile Asp Ser Val Ala Gly Ile Asn Tyr Gly Leu
195 200 205

Val Ala Pro Pro Ala Thr Thr Ala Glu Thr Leu Asp Val Gln Met Lys
210 215 220 225

Gly Glu Phe Tyr Ser Glu Asn His His Asn Pro Pro Pro Phe Ala Pro
230 235 240

Pro Val Met Glu Phe Pro Ala Ala His Asp Arg Met Val Tyr Leu Gly
245 250 255

Leu Ser Asp Tyr Phe Phe Asn Thr Ala Gly Leu Val Tyr Gln Glu Ala
260 265 270

Gly Val Leu Lys Met Thr Leu Arg Asp Asp Met Ile Pro Lys Glu Ser
275 280 285

Lys Phe Arg Leu Thr Thr Lys Phe Phe Gly Thr Phe Leu Pro Glu Val
290 295 300 305

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Ala Lys Lys Phe Pro Asn Met Lys Ile Gln Ile His Val Ser Ala Ser
310 315 320

Thr Pro Pro His Leu Ser Val Gln Pro Thr Gly Leu Thr Phe Tyr Pro
325 330 335

Ala Val Asp Val Gln Ala Phe Ala Val Leu Pro Asn Ser Ser Leu Ala
340 345 350

Ser Leu Phe Leu Ile Gly Met His Thr Thr Gly Ser Met Glu Val Ser
355 360 365

Ala Glu Ser Asn Arg Leu Val Gly Glu Leu Lys Leu Asp Arg Leu Leu
370 375 380 385

Leu Glu Leu Lys His Ser Asn Ile Gly Pro Phe Pro Val Glu Leu Leu
390 395 400

Gln Asp Ile Met Asn Tyr Ile Val Pro Ile Leu Val Leu Pro Arg Val
405 410 415

Asn Glu Lys Leu Gln Lys Gly Phe Pro Leu Pro Thr Pro Ala Arg Val
420 425 430

Gln Leu Tyr Asn Val Val Leu Gln Pro His Gln Asn Phe Leu Leu Phe
435 440 445

Gly Ala Asp Val Val Tyr Lys
450 455

Application Published

CLAIMS

What Is Claimed Is:

1. Use of atomic coordinates of bactericidal/permeability-increasing ("BPI") protein, or fragment, analog or variant thereof, to model a BPI protein.

2. Use of atomic coordinates of bactericidal/permeability-increasing ("BPI") protein, or fragment, analog or variant thereof, to model a BPI-related lipid transfer protein.

3. The use according to claim 2, wherein the BPI-related lipid transfer protein is lipopolysaccharide-binding protein (LBP), cholesteryl ester transferase protein (CETP) or phospholipid transfer protein (PLTP), or fragment, analog or variant thereof.

4. The use according to any of claims 1-3, wherein the BPI protein comprises a binding site characterized by amino acid residues of at least one binding pocket as defined in Table 31.

5. The use according to any of claims 1-3, wherein the BPI protein comprises a binding site characterized by at least one amino acid sequence, or variant of the sequence, selected from positions about 17 to about 45, positions about 36 to about 54, positions about 65 to about 99, positions about 84 to about 109, positions about 142 to about 164, or positions about 142 to about 169 of BPI.

6. The use according to any of claims 1-3, wherein the BPI protein comprises a binding site characterized by amino acid residues of at least one binding pocket as defined in Table 3 and a binding site characterized by at least one amino acid sequence, or variant of the sequence, selected from positions about 17 to about 45, positions about 36 to about 54, positions about 65 to about 99, positions about 84 to about 109, positions about 142 to about 164, or positions about 142 to about 169 of BPI.

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7. Use of atomic coordinates of bactericidal/permeability-increasing ("BPI") protein to computationally design a chemical compound for mimicking BPI protein, or fragment, analog or variant thereof.

8. Use of atomic coordinates of bactericidal/permeability-increasing ("BPI") protein to computationally design a chemical compound for mimicking a BPI-related lipid transfer protein, or fragment, analog or variant thereof.

9. The use according to claim 8, wherein the BPI-related lipid transfer protein is lipopolysaccharide-binding protein (LBP), cholesteryl ester transferase protein (CETP) or phospholipid transfer protein (PLTP).

10. Use of atomic coordinates of bactericidal/permeability-increasing ("BPI") protein, to design a chemical compound capable of associating with a BPI-related lipid binding protein, or fragment, analog or variant thereof.

11. The use according to claim 10, wherein the BPI-related lipid binding protein is lipopolysaccharide-binding protein (LBP), cholesteryl ester transferase protein (CETP) or phospholipid transfer protein (PLTP), or fragment, analog or variant thereof.

12. Use of atomic coordinates of bactericidal/permeability-increasing ("BPI") protein to design a model of ligands in an active site of a lipid binding protein.

13. The use according to claim 12, wherein the lipid binding protein is bactericidal/permeability-increasing protein (BPI), lipopolysaccharide-binding protein (LBP), cholesteryl ester transferase protein (CETP) or phospholipid transfer protein (PLTP), or fragment, analog or variant thereof.

14. Use of atomic coordinates of bactericidal/permeability-increasing ("BPI") protein, to design compounds with at least one activity selected from the group consisting of antibacterial, antifungal, antimycobacterial, antichlamydial, antiprotozoan, heparin-binding, endotoxin-binding, heparin-neutralizing, endotoxin-neutralizing, inhibition of tumor and

endothelial cell proliferation, inhibition of angiogenesis, anti-inflammatory, anticoagulant and antithrombolytic.

15. The use according to any of claims 1 - 14, wherein said atomic coordinates are according to Table 4.

16. A method of three-dimensional modeling of a bactericidal/permeability-increasing ("BPI") protein comprising the steps of:

(a) providing three-dimensional atomic coordinates derived from X-ray diffraction measurements of a BPI protein in a computer readable format;

(b) inputting the data from step (a) into a computer with appropriate software programs;

(c) generating a three-dimensional structural representation of the BPI protein suitable for visualization and further computational manipulation.

17. A method of three-dimensional modeling of a bactericidal/permeability-increasing ("BPI")-related lipid transfer protein comprising the steps of:

(a) providing three-dimensional atomic coordinates derived from X-ray diffraction measurements of a BPI protein in a computer readable format;

(b) inputting the data from step (a) into a computer with appropriate software programs;

(c) generating a three-dimensional structural representation of the BPI-related lipid transfer protein suitable for visualization and further computational manipulation.

18. The use according to any of claims 16-17, wherein the BPI protein comprises a binding site characterized by amino acid residues of at least one binding pocket as defined in Table 3.

19. The use according to any of claims 16-17, wherein the BPI protein comprises a binding site characterized by at least one amino acid sequence, or variant of the sequence, selected from positions about 17 to about 45, positions about 36 to about 54, positions about

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65 to about 99, positions about 84 to about 109, positions about 142 to about 164, or positions about 142 to about 169 of BPI.

20. The use according to any of claims 16-17, wherein the BPI protein comprises a binding site characterized by amino acid residues of at least one binding pocket as defined in Table 3 and a binding site characterized by at least one amino acid sequence, or variant of the sequence, selected from positions about 17 to about 45, positions about 36 to about 54, positions about 65 to about 99, positions about 84 to about 109, positions about 142 to about 164, or positions about 142 to about 169 of BPI.

21. A method for providing an atomic model of a BPI protein, or fragment, analog or variant thereof, comprising

(a) providing a computer readable medium having stored thereon atomic coordinate/x-ray diffraction data of the BPI protein, or fragment, analog or variant thereof, in crystalline form, the data sufficient to model the three-dimensional structure of the BPI protein, or fragment, analog or variant thereof;

(b) analyzing, on a computer using at least one subroutine executed in said computer, atomic coordinate/x-ray diffraction data from (a) to provide atomic coordinate data output defining an atomic model of said BPI protein, or fragment, analog or variant thereof, said analyzing utilizing at least one computing algorithm selected from the group consisting of data processing and reduction, auto-indexing, intensity scaling, intensity merging, amplitude conversion, truncation, molecular replacement, molecular alignment, molecular refinement, electron density map calculation, electron density modification, electron map visualization, model building, rigid body refinement, positional refinement; and

(c) obtaining atomic coordinate data defining the three-dimensional structure of at least one of said BPI protein, or fragment, analog or variant thereof.

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22. A method according to claim 21, wherein said computer readable medium further has stored thereon data corresponding to a nucleic acid sequence or an amino acid sequence data comprising at least one structural domain or functional domain of a BPI, LBP, CETP or PLTP corresponding to at least one BPI or mutant primary sequence of Figures 2-20 or Table 2, or a fragment thereof; and wherein said analyzing step further comprises analyzing said sequence data.

23. A computer-based system for providing atomic model data of the three-dimensional structure of BPI protein, or fragment, analog or variant thereof, a BPI mutant or a BPI fragment, comprising the following elements:

(a) at least one computer readable medium (CRM) having stored thereon atomic coordinate/x-ray diffraction data of said BPI protein, or fragment, analog or variant thereof;

(b) at least one computing subroutine that, when executed in a computer, causes the computer to analyze atomic coordinate/x-ray diffraction data from (a) to provide atomic coordinate data output defining an atomic model of said BPI protein, or fragment, analog or variant thereof, said analyzing utilizing at least one computing subroutine selected from the group consisting of data processing and reduction, auto-indexing, intensity scaling, intensity merging, amplitude conversion, truncation, molecular replacement, molecular alignment, molecular refinement, electron density map calculation, electron density modification, electron map visualization, model building, rigid body refinement, positional refinement; and

(c) retrieval means for obtaining atomic coordinate output data substantially defining the three-dimensional structure of said BPI protein, or fragment, analog or variant thereof.

24. A method for providing a computer atomic model of a ligand of a BPI protein, or fragment, analog or variant thereof, comprising

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(a) providing a computer readable medium (CRM) having stored thereon atomic coordinate data of a BPI protein, or fragment, analog, or variant thereof;

(b) providing a CRM having stored thereon atomic coordinate data sufficient to generate atomic models of potential ligands of said BPI protein, or fragment, analog, or variant thereof;

(c) analyzing on a computer, using at least one subroutine executed in said computer, the atomic coordinate data from (a) and ligand data from (b), to determine binding sites of BPI protein, or fragment, analog, or variant thereof, and to provide atomic coordinate data defining an atomic model of at least one ligand of said BPI, BPI mutant or a fragment thereof, said analyzing utilizing computing subroutines selected from the group consisting of data processing and reduction, auto-indexing, intensity scaling, intensity merging, amplitude conversion, truncation, molecular replacement, molecular alignment, molecular refinement, electron density map calculation, electron density modification, electron map visualization, model building, rigid body refinement, positional refinement; and

(d) obtaining atomic coordinate model output data defining the three-dimensional structure of said at least one ligand of said BPI protein, or fragment, analog, or variant thereof.

25. A computer-based system for providing an atomic model of at least one ligand of a BPI, BPI mutant or a fragment thereof, comprising the following elements;

(a) a computer readable medium (CRM) having stored thereon atomic coordinate data of a BPI, mutant or fragment thereof;

(b) a CRM having stored thereon atomic coordinate data sufficient to generate atomic models of potential ligands of a BPI, mutant or fragment;

(c) at least one computing subroutine for analyzing on a computer, the atomic coordinate data from (a) and (b), to determine binding sites of BPI protein, or fragment, analog, or variant thereof, and to provide

data output defining an atomic model of at least one potential ligand of BPI protein, or fragment, analog, or variant thereof, said analyzing utilizing at least one computing subroutine selected from the group consisting of data processing and reduction, auto-indexing, intensity scaling, intensity merging, amplitude conversion, truncation, molecular replacement, molecular alignment, molecular refinement, electron density map calculation, electron density modification, electron map visualization, model building, rigid body refinement, positional refinement; and

(d) retrieval means for obtaining atomic coordinate data of said at least one ligand of a BPI protein, or fragment, analog or variant thereof.

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Abstract

The present invention solves the three-dimensional structure of BPI and thereby provides atomic coordinates of BPI from the analysis of x-ray diffraction patterns of sufficiently high resolution for three-dimensional structure determination of the protein, as well as methods for rational drug design, based on using amino acid sequence data and/or x-ray diffraction data provided on computer readable media, as analyzed on a computer system having suitable computer algorithms; and atomic coordinates are provided yielding structural information on related proteins, including the lipid binding and lipid transport protein family that includes BPI, LBP, CETP and PLTP.

Doc # 2015154.2

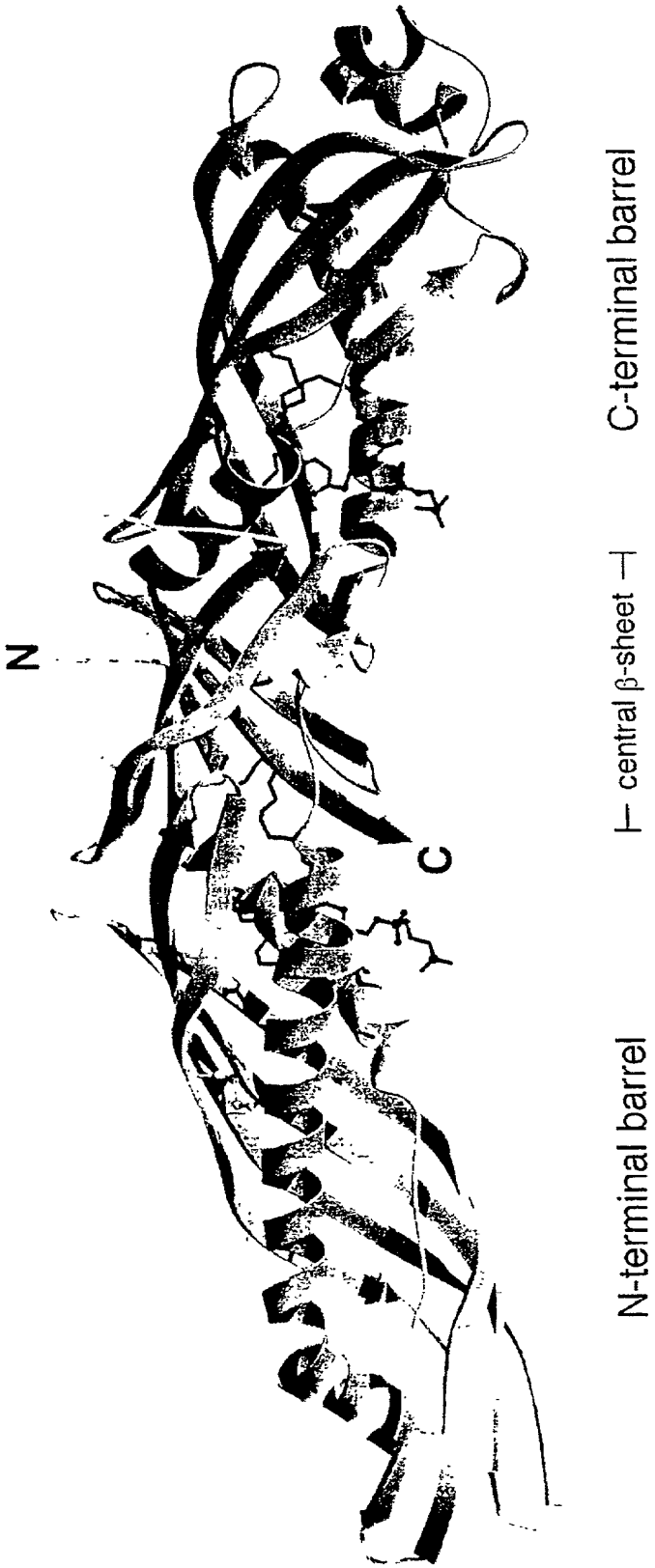

Fig. 1A

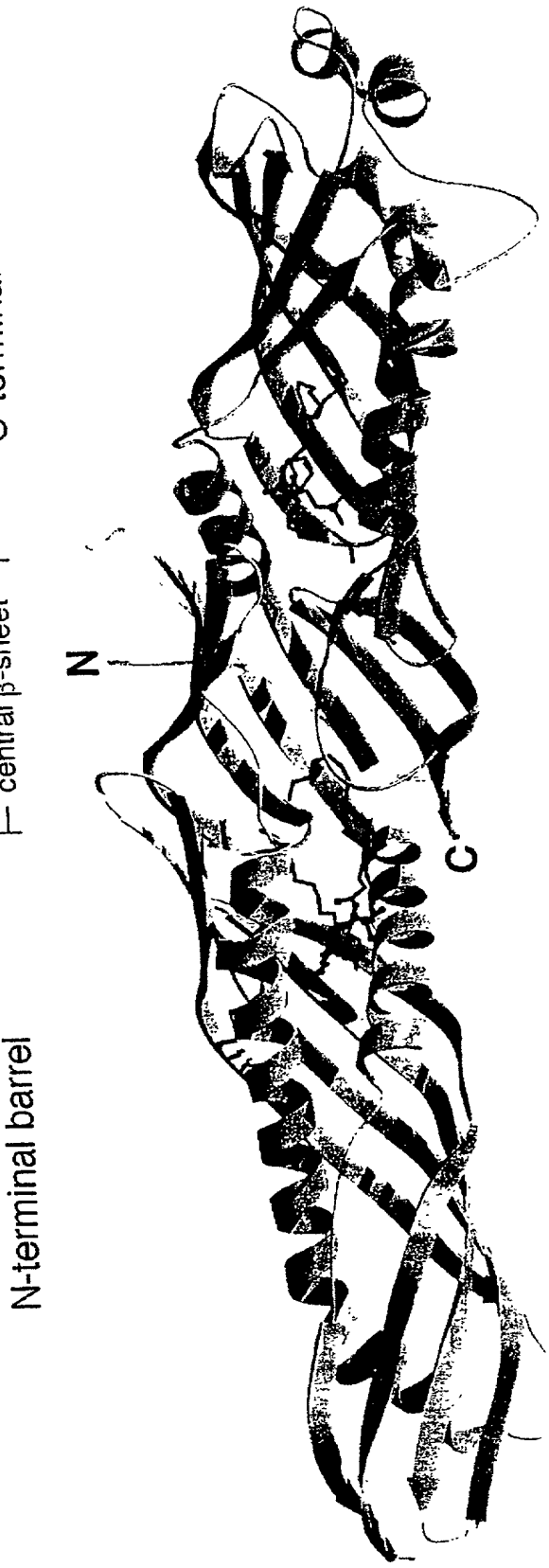

Fig. 1B

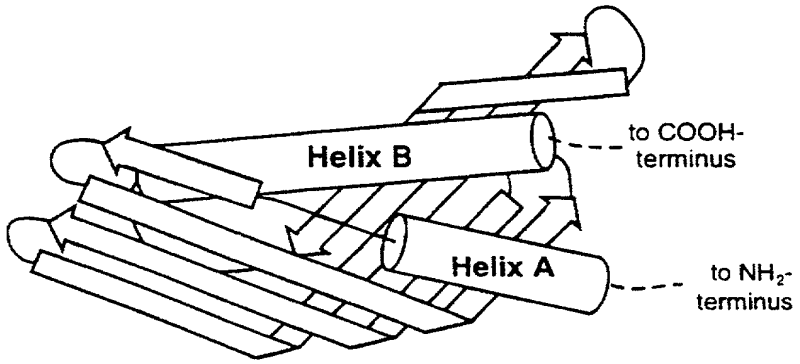

Fig. 2A

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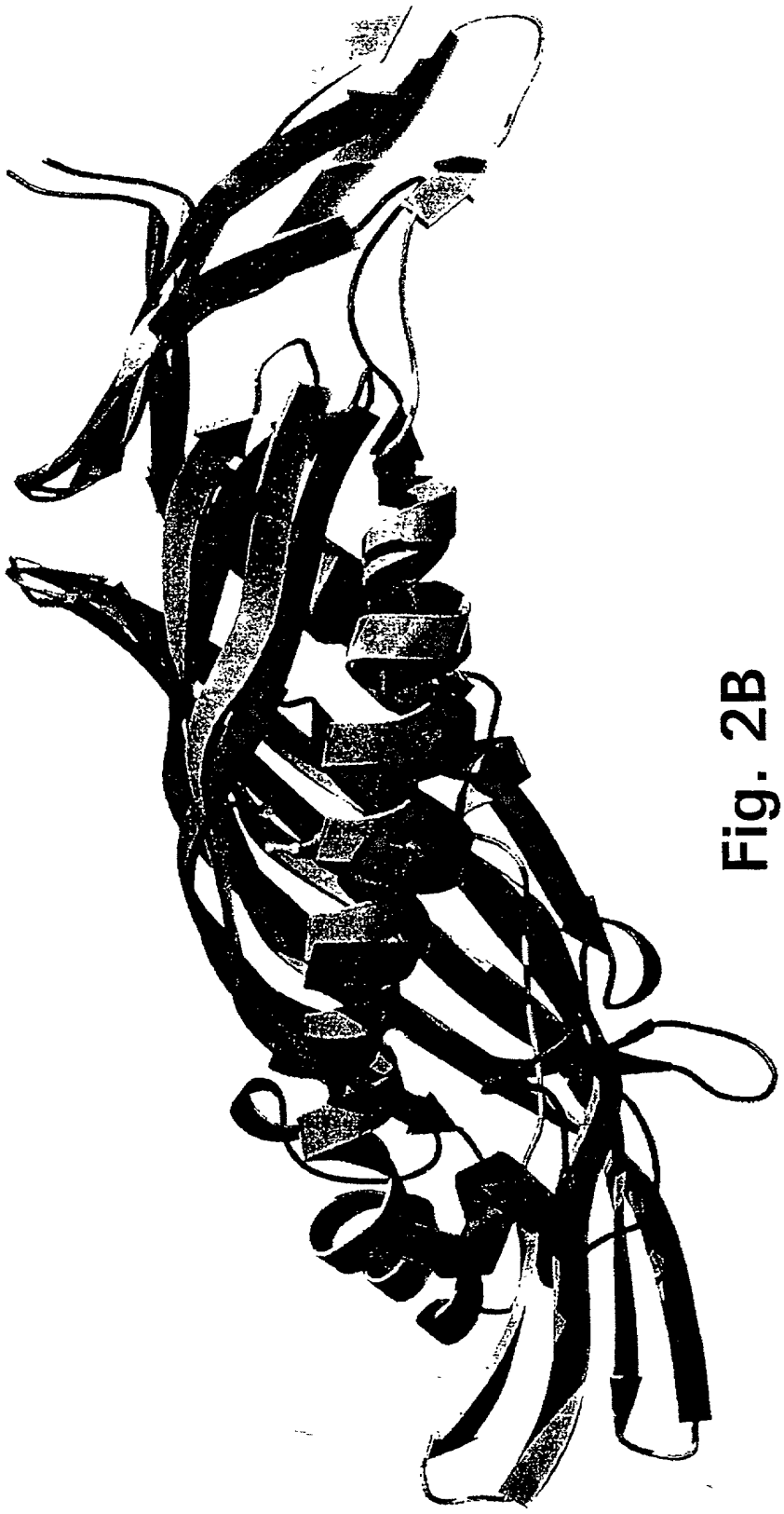


Fig. 2B

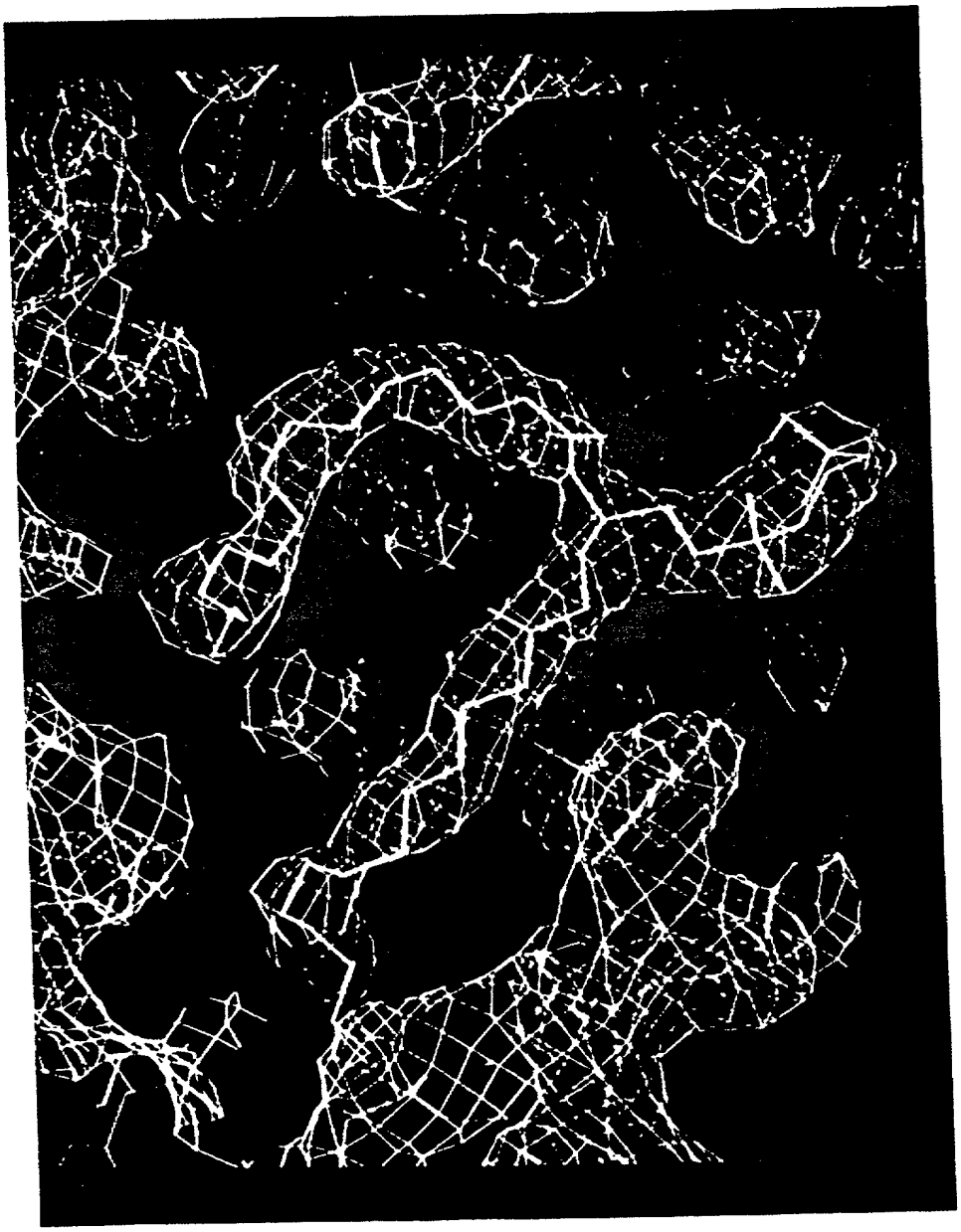


Fig. 3

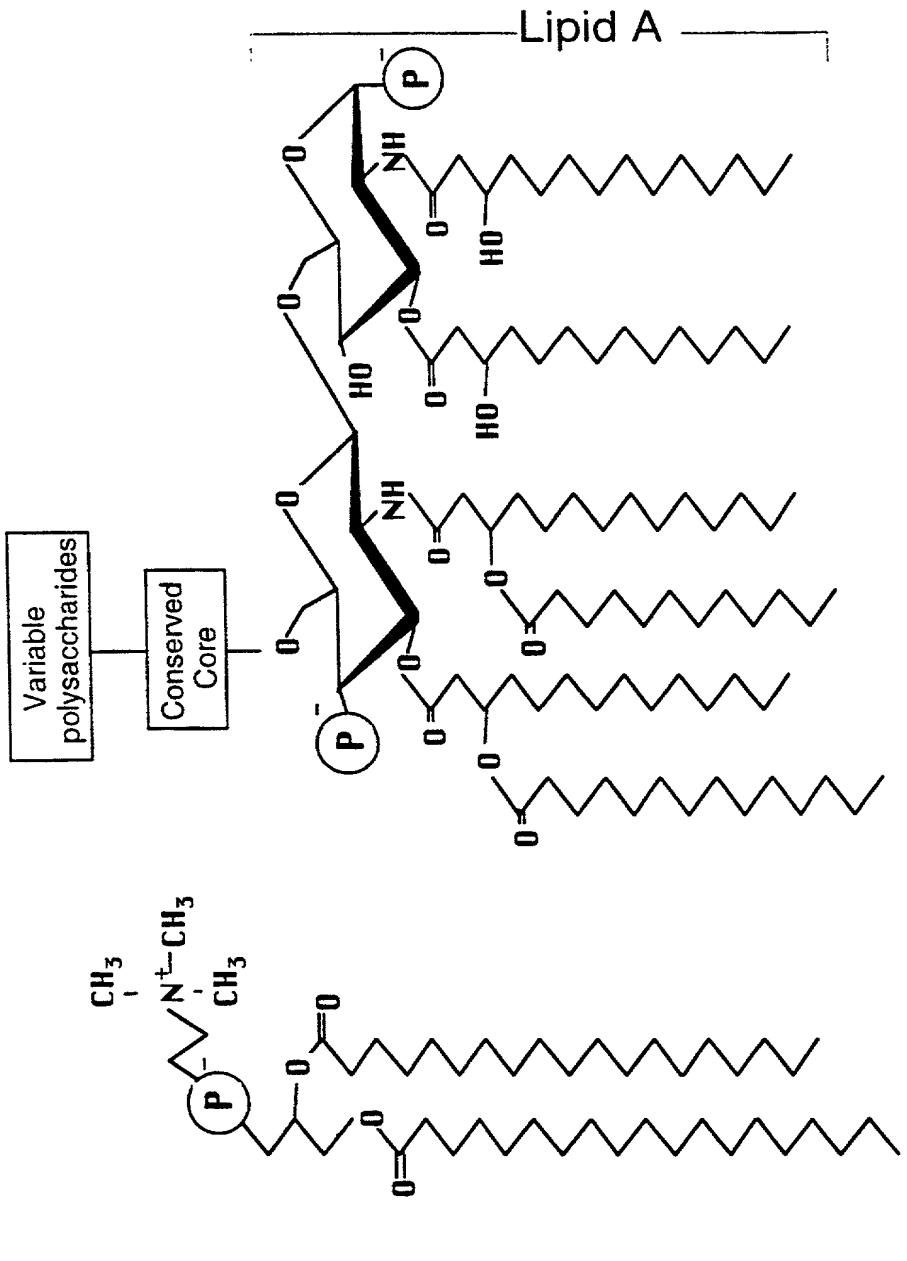

Lipid A
Variable polysaccharides
Conserved Core
LPS
Phosphatidylcholine

Fig. 4A

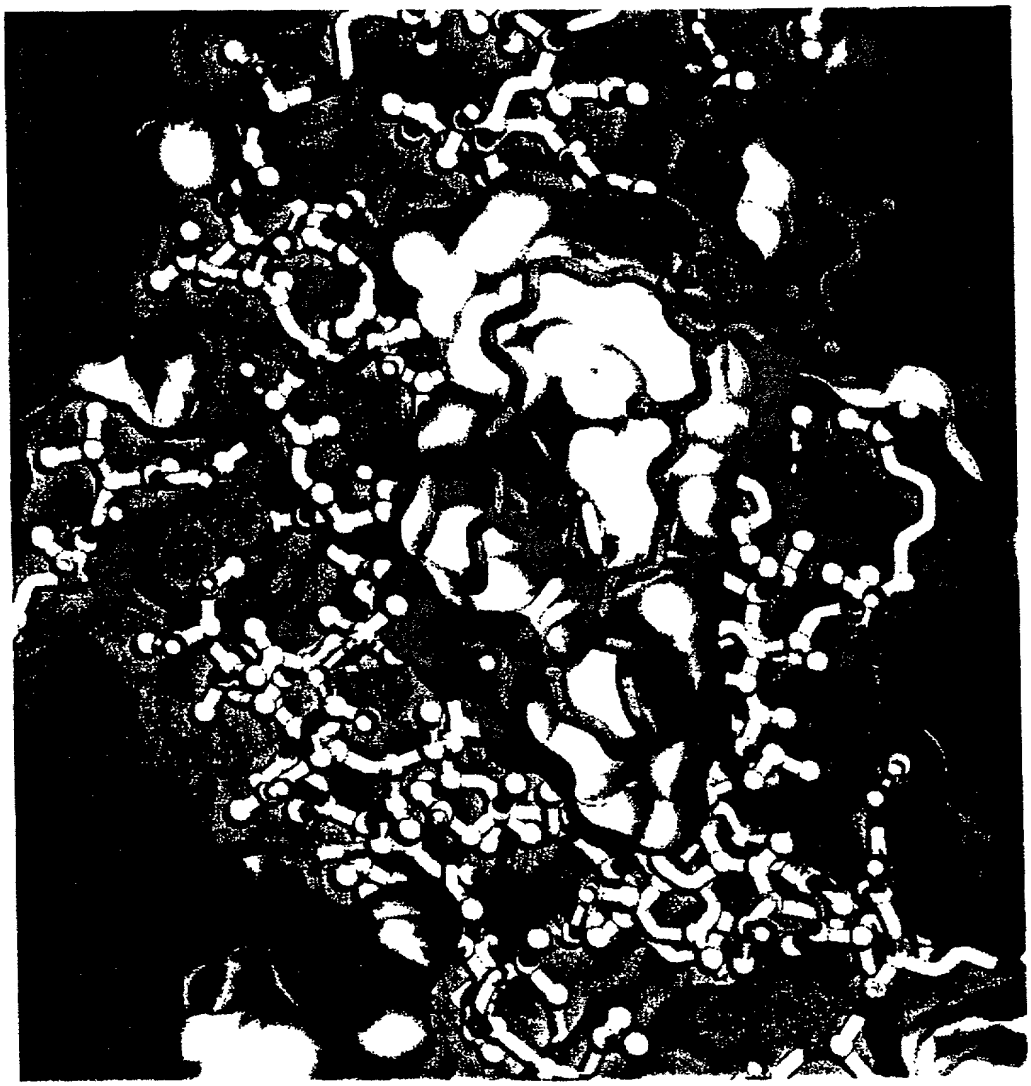
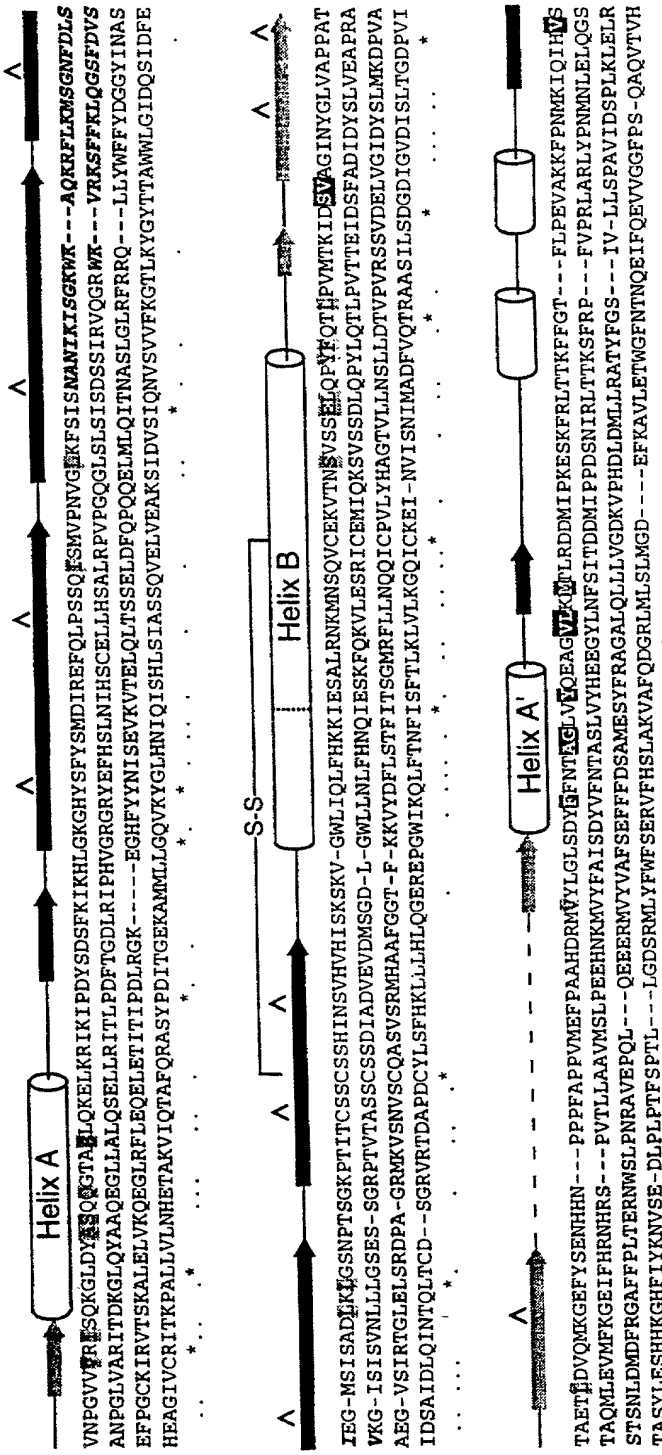


Fig. 4B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S-S
Helix B
Helix A'
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PLTP EFPGCKIRVTSKALELVKQEGLRFLEQELETITIPDLRGK-----EGHFYYNISEVKVTELQLTSSELDFQPQQELMLQITNASLGLRFRRQ---LLYWFFYDGGYINAS 102
CETP HEAGIVCRITKPALLVLNHETAKVIQTAFQRASYPDITGEKAMMLLGQVKYGLHNIQISHLSIASSQVELVEAKSIDVSIQNVSVVFKGTLKYGYTTAWWLGIDQSIDFE 110
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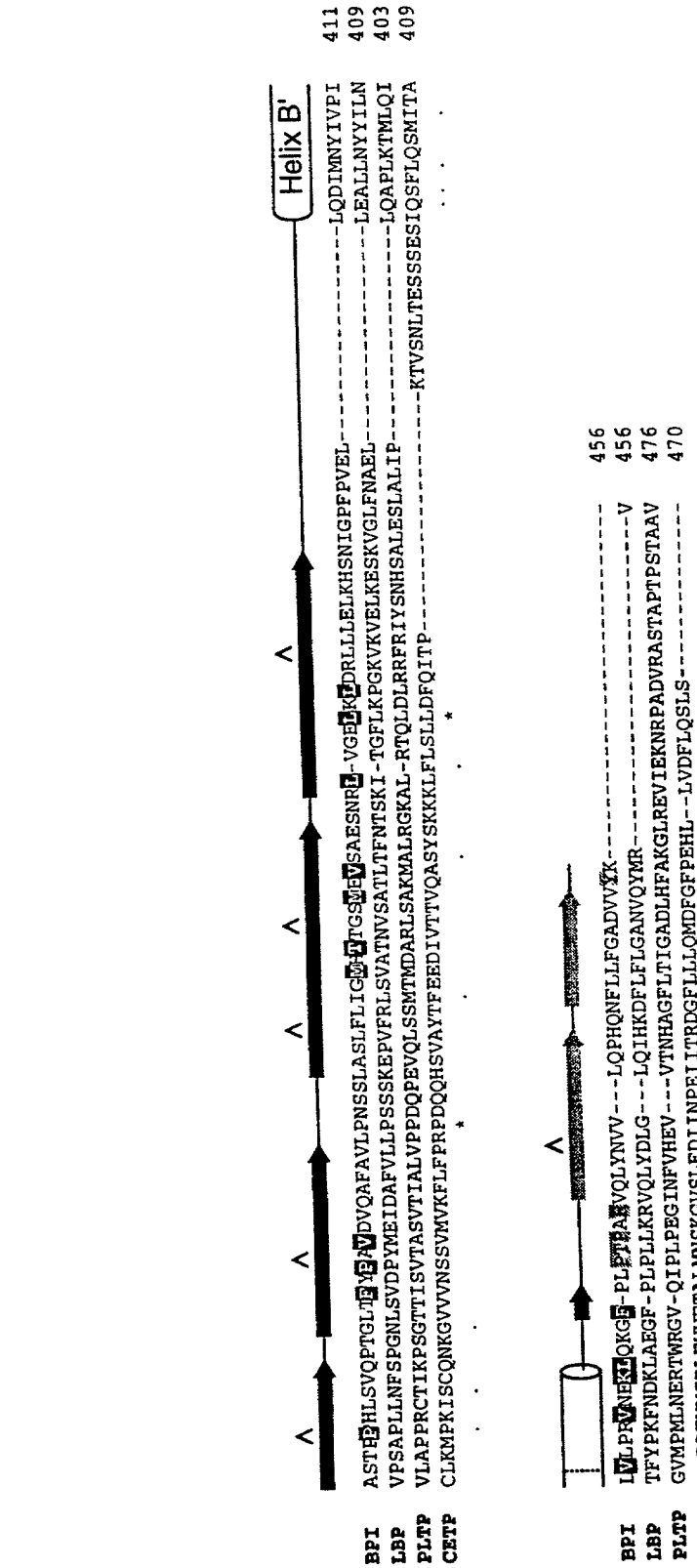
CETP TASYLESHHKGHFIYKNVSE-DLPLPTFSPTL---LGDSRMLYFWFSERVFHSLAKVAFQDGRLMLSLMGD---EFKAVLETWGFNTNQEIFQEVVGGFPS-QAQVTVH 318

Fig. 5A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PLTP VLAPPRCTIKPSGTTISVTASVTIALVPPDQPEVQLSSMTMDARLSAKMALRGKAL-RTQLDLRRFRIYSNHSALESLALIP----------LQAPLKTMLQI 403
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LBP TFYPKFNDKLAEGF-PLPLLKRVQLYDLG---LQIHKDFLFLGANVQYMR---------- 456
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Fig. 5B

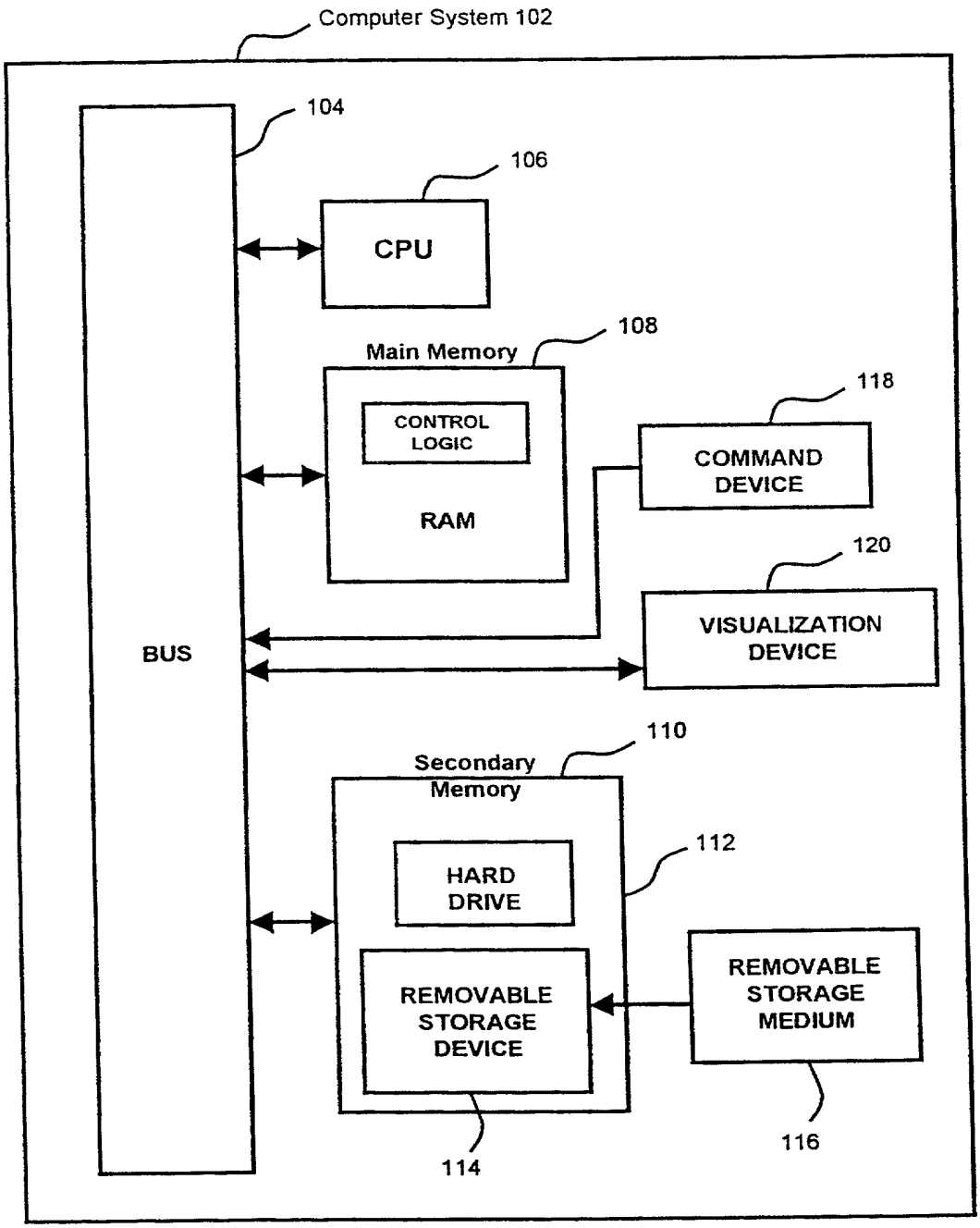
Computer System 102
104
106
CPU
108
Main Memory
CONTROL LOGIC
RAM
118
COMMAND DEVICE
120
VISUALIZATION DEVICE
BUS
110
Secondary Memory
112
HARD DRIVE
REMOVABLE STORAGE DEVICE
REMOVABLE STORAGE MEDIUM
114
116

Fig. 6

DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY

As below named inventor(s), I/we hereby declare that my/our residence(s), post office address(es) and citizenship are as stated below next to my/our name(s); I/we believe that I/we am/are the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled, **"BACTERICIDAL/PERMEABILITY-INCREASING PROTEIN: CRYSTALLIZATION, X-RAY DIFFRACTION, THREE-DIMENSIONAL STRUCTURE DETERMINATION, RATIONAL DRUG DESIGN AND MOLECULAR MODELING OF RELATED PROTEINS"** the specification of which was filed on June 22, 1998 as U.S. Application Serial No. 09/446,415 and was amended on _____ (if applicable); ☒ was filed as PCT International Application No. PCT/US98/13007 on June 22, 1998 and was amended under Article 19 on _____ (if applicable). I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in 37 C.F.R. §1.56.

I/we hereby claim foreign priority benefits under 35 U.S.C. §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

(Application Serial Number)	(Country)	(Day/Month/Year Filed)	Priority Claimed Yes	Priority Claimed No
			☐	☐

☐ I/we hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below:

(Application Serial Number)	(Day/Month/Year Filed)

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(Application Serial Number)	(Day/Month/Year Filed)	(Status-Patented, Pending or Abandoned)
PCT/US98/13007	22 June 1998	

I/we hereby declare that all statements made herein of my/our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: I hereby appoint as my attorneys, with full powers of substitution and revocation, to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

Janet M. McNicholas, Ph.D. (32,918) of McAndrews, Held & Malloy, Ltd., 500 West Madison Street, 34th Floor, Chicago, IL 60661

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Full Name of First or Sole Inventor	Citizenship
Lesa J. Beamer	United States of America
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City (Zip)	City (Zip)
Columbia 65203	Columbia 65203
State or Country	State or Country
Missouri	Missouri
Date	Signature
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☒ See second page for additional inventor(s)

See reverse for relevant rules & statutes

Second Joint Inventor, if any Stephen F. Carroll	Citizenship United States of America
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Date ☒	Signature ☒

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City (Zip)	City (Zip)
State or Country	State or Country
Date ☒	Signature ☒

Fifth Joint Inventor, if any	Citizenship
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City (Zip)	City (Zip)
State or Country	State or Country
Date ☒	Signature ☒

Sixth Joint Inventor, if any	Citizenship
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City (Zip)	City (Zip)
State or Country	State or Country
Date ☒	Signature ☒

Seventh Joint Inventor, if any	Citizenship
Residence Address - Street	Post Office Address - Street
City (Zip)	City (Zip)
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Atty. Docket No: 11034US02 / 100-248.P1

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State or Country Missouri	State or Country Missouri
Date ☒	Signature ☒

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See reverse for relevant rules & statutes

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State or Country California	State or Country California
Date ☒ 6-5-00	Signature ☒ David Eisenberg

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State or Country	State or Country
Date ☒	Signature ☒

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State or Country	State or Country
Date ☒	Signature ☒

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State or Country	State or Country
Date ☒	Signature ☒

Seventh Joint Inventor, if any	Citizenship
Residence Address - Street	Post Office Address - Street
City (Zip)	City (Zip)
State or Country	State or Country
Date ☒	Signature ☒

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Atty. Docket No: 11034US02 / 100-248.P1

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State or Country	**State or Country**
Missouri	Missouri
Date ☒ 3/29/00	**Signature** ☒ Lesa J Beamer

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See reverse for relevant rules & statutes

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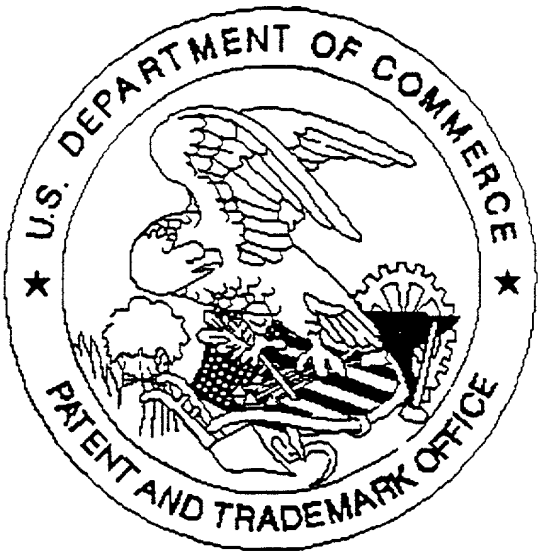

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